EVENT REPORT

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EFSA Scientific Workshop, co-sponsored by FAO and WHO

Revisiting the International Estimate of Short-Term Intake (IESTI equations) used to estimate the acute exposure to pesticide residues via food

8/9 September 2015
Geneva, Switzerland

European Food Safety Authority
and the Dutch National Institute for Public Health and the Environment (RIVM)

Abstract

EFSA organised a Scientific Workshop to discuss the possible revision of the methodology used for estimating short-term dietary exposure to pesticide residues (IESTI equations). The event was co-sponsored by FAO and WHO and took place from 8 to 9 September 2015 in Geneva. Almost 40 participants from approximately 20 countries representing European and non-European risk assessment and risk management regulatory bodies, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), food inspection services and other bodies contributed to the discussion. The workshop was structured in plenary discussions and break-out sessions where possible ways to harmonise the methodology were discussed. Following the expert discussions a set of recommendations was derived that will be further discussed with JMPR, national and regional food safety authorities and risk managers in view of adoption of a renewed IESTI methodology.

Key words: pesticides, residues, short-term dietary exposure assessment, IESTI equation, variability factor, unit weight, large portion

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Correspondence: any enquires related to this output should be addressed to pesticides.mrl@efsa.europa.eu

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Summary

The IESTI (International Estimate of Short-Term Intake) methodology was first described in the report of a FAO/WHO consultation which took place in Geneva in 1997 and a subsequent meeting in 1999. Since then, the methodology has been used by many regulatory authorities responsible for setting legal limits at national or regional level and by the JMPR to perform the risk assessment in the framework of the MRL setting by the Codex Committee on Pesticide Residues.

Since its development the methodology was modified several times by the JMPR, but not all modifications have been taken over in all parts of the world, in particular in the EU. This results in the fact that the acute risk assessment approaches used by different risk assessment bodies are currently not fully harmonised.

Although the IESTI equations have been developed to be used in the framework of MRL setting, it turned out that there is also a need to perform exposure/risk assessments at enforcement level (food inspection services). Thus, the IESTI was also used by food safety inspection services to assess the risk for consumers of actual residue levels measured in food commodities.

EFSA organised a stakeholder meeting on 7 September 2015 in order to collect the different views of stakeholders and interested parties on the current methodology for calculating the short-term dietary intake and on possible changes to this methodology. Representatives of risk management bodies, of producing and exporting countries, of NGOs, of Industry have been invited to this stakeholder meeting and some kindly accepted to speak about their expectations in the context of the harmonisation of the IESTI methodology. The purpose of the stakeholder meeting was to collect as completely as possible all these views and contributions in order to use this input in a scientific workshop co-sponsored by EFSA, FAO and WHO and taking place immediately after this meeting.

The Scientific Workshop following the stakeholder meeting was organised to allow experts working in the field of dietary exposure assessment of pesticide residues to reflect on the necessity and the different options to modify the currently used risk assessment methodology. The current event report summarises the discussions and conclusions together with the recommendations to serve as a basis for further discussion by the JMPR, national and regional food safety authorities and risk managers in view of the adoption of a renewed IESTI methodology.

The workshop participants agreed on the revised equations, to simplify and harmonise the current methodology based on knowledge gained through experience and on future work required.

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1. Introduction

The methodology for calculating the acute dietary exposure to pesticide residues in the context of MRL setting was initially developed at two meetings in the late 1990s (WHO, 1997, FAO, 1999). The methodology known as the IESTI calculation is the International Estimation of Short-Term Intake.

Subsequently, the methodology was further developed by JMPR. In 2002 and 2003, JMPR implemented a change in the IESTI equation, involving the lowering of the variability factor to a default value of 3 for those commodities calculated using the case 2 equations, i.e. commodities with a unit weight of more than 25 g (FAO, 2002, 2003).

The EU Member States expressed a reservation on this modification in 2004 (FAO/WHO, 2004), pending internal evaluation of this change. Subsequently, the Panel on Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA) has adopted a scientific opinion on the variability factors used in the IESTI equation (EFSA, 2005), recommending a reconsideration of the variability factors used, while taking into account the desired conservatism; EU risk managers were reluctant to amend the variability factors at the time without having a full impact assessment of the possible modifications.

Thus, within the EU, EFSA was requested to provide a second opinion, including an assessment of the estimation of the conservatism of the IESTI equation with respect to the percentage of the total European population protected. In addition, a sensitivity analysis was requested to determine the effect of replacing the HR with other estimates of the highest residues, e.g. the MRL should be assessed. Following discussion on the opinion of EFSA, published in 2007 (EFSA, 2007), the European Commission put forward a proposal to change the IESTI equation as implemented within the EU by simultaneously replacing the HR with the MRL and using a default variability factor of 3 instead of 5 and 7. However, a final agreement on this proposal was not reached at the time.

At several of its meetings, JMPR has indicated the need for an international meeting to revisit the IESTI equation. In 2006, inter alia, the following specific issues were identified that should be further discussed (FAO, 2006):

- Uncertainty and variability of the parameters used in the estimation;
- Ways to improve the consumption, unit weight and body weight data provided to JMPR;
- Identification of additional subgroups of the population for which the assessment should be conducted, e.g. toddlers;
- The adequacy of the IESTI equation when residues from monitoring/enforcement data are used or the need for specific methodology for this type of application;
- How to improve communication between the JMPR, the risk managers and the public on the output of the risk assessment conducted by JMPR.

In 2007 JMPR concluded that, overall, the IESTI (using the HR as an input) is a satisfactory indicator for assessing the short-term dietary intake and the acceptability of MRLs. However, from the perspective of public perception there may be benefits in estimating the IESTI using the MRL, while also including adjustments for edible portion and the different residue definitions for risk assessment and enforcement. The previously made recommendation to organise a consultation, including relevant stakeholders was reiterated. The main objective of such an event would be the continued refinement of the estimation of the short-term dietary intake of pesticides and of the interpretation of the outcome of short-term dietary risk assessments conducted by JMPR. Furthermore JMPR recommended discussing whether it is appropriate to use the IESTI equation for evaluating the safety of individual consignments (FAO, 2007).

The discussion on the IESTI methodology was continued in 2010 (FAO, 2010), where particular emphasis was put on the issue of uncertainties in the calculation of the IESTI. JMPR stressed the fact that to ensure international harmonisation of the methodology, changes such as a possible replacement of HR by MRL in the IESTI equations cannot be implemented by JMPR alone, but should be discussed, as recommended previously, at the international level.

Since not all modifications previously introduced by JMPR have been adopted in all parts of the world (e.g. in the EU), the risk assessment approaches currently used by different risk assessment bodies are not fully harmonised, leading to the fact that Codex Maximum Residue Limits (CXLs) are not adopted by all Codex member countries ultimately leading to possible trade disruptions.

There is also a need to perform short-term dietary exposure assessments at the enforcement level to decide whether consignments containing pesticide residues, in particular residues exceeding the legal limits, is unsafe need to be destroyed or withdrawn fro m the market because of possible consumer health risks.[1]

EFSA and the Dutch WHO Collaborating Centre on Chemical Food Safety (RIVM) decided to organise a Scientific Workshop to seek the views of experts on the methodology. Individuals in the field of dietary exposure assessment of pesticide residues representing different geographic and economic regions attended, with the aim of proposing recommendations for harmonising the methodology. FAO and WHO co-sponsored this event.

The overall goal of the Scientific Workshop wa s to evaluate and where possible harmonise the parameters within the IESTI equations as well as the equations themselves in order to propose ways to refine the methodology. In addition, the appropriateness of the IESTI methodology in assessing residues from monitoring and enforcement programmes was considered. In preparation for the workshop, experts of the Dutch National Institute for Public Health and the Environment (RIVM) drafted a background document describing the issues to be discussed a nd proposals for possible ways forward. In particular the following key questions were identified for further discussion by the experts.

- What would be the appropriate IESTI equation(s)?
- Is there an acceptance to assess the safety of the MRL instead of the highest residue (HR) observed in the set of supervised field trials submitted by applicants?
- Is the concept of including the Unit weight in the short -term dietary exposure assessment appropriate?
- Which variability factor should be used in the IESTI equation(s) for different crops/crop types?
- Is there the need to include other variables in the IESTI equation(s) (conversion factors for risk assessment residue definitions, processing factors)?
- How to deal with situations where the residues are below the limit of quantification (LOQ)?
- How to deal with animal commodities?
- Would it be desirable to define a harmonized worldwide large portion (LP), i.e. the worst case food consumption for each food product for which short -term dietary exposure assessments should be performed?
- How should the LP be calculated? What is the appropriate IESTI equation for food safety inspection services?
- How to make the required input parameters available (e.g. processing factors, conversion factors)
- How would the level of protection b e affected by the proposed changes in the IESTI equation?
- Would the proposed changes in the IESTI equation give the same level of protection?

To gain the broadest possible input for reconsidering the IESTI equations, EFSA organised a stakeholder meeting on the day before the Scientific Workshop (7 September 2015), to provide an opportunity for all stakeholders (e.g. representatives of civil society, institutional stakeholder, industry and academia) to present their views and to identify shortcomings on t he currently used methodology for acute exposure assessment. All interested stakeholders who registered for the event were invited.

[1] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authori ty and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24

[2] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

[3] Surrogate MRL (as defined in the Background document, see Annex A): a high residue corresponding to the true MRL but

The list of participating stakeholders and the key discussion points raised during the Stakeholder Meeting are included in Annex B. The stakeholder meeting was opened by Dr. Juliane Kleiner (EFSA) who highlighted the importance of the IESTI methodology for EFSA and the desire of EFSA to contribute to the scientific discussion on the IESTI methodology for the purposes of harmonisation. Dr. Angelika Tritscher (WHO) in her welcoming remarks appreciated the need to harmonise the risk assessment methodology at international level and EFSA's initiative towards this important aim.

On 8 September 2015, the Scientific Workshop was opened by Dr. Kazuaki Miyagishima, Director, Department of Food Safety and Zoonoses, Health Security and Environment (World Health Organisation (WHO) on behalf of FAO and WHO and Luc Mohimont, Deputy Head of the Pesticides Unit (European Food Safety Authority). Dr Kazuaki Miyagishima welcomed and thanked the participants on behalf of the Assistant Directors General of FAO and WHO. He emphasized that scientific advice was amongst the top priorities for the two agencies and that it was important to continuously improve the methodologies to assess the risk related to hazards in food. Dr Miyagishima reminded the meeting that the world was scrutinising the quality of the scientific advice to support food safety standards and stressed the value of facilitating convergence in acute risk assessment methodologies and outcomes. He wished all participants a successful meeting. Luc Mohimont highlighted that providing support for scientific cooperation between the European Community, international organisations and third countries is an important mission for EFSA. Therefore EFSA organised the scientific workshop bringing together almost 40 scientists from all over the world. The purpose of the workshop was to derive recommendations striving for international harmonisation and taking the views expressed during the stakeholder meeting into account.

2. Working methodology of the workshop

During the workshop the participants discussed in detail the questions raised in the background document taking into account the outcomes of the stakeholder meeting (see Annex A and Annex B). Considering the number of participants, the discussions were conducted in two breakout groups. The results of the two groups were then brought back to the plenary meeting where the final conclusions were derived.

The conclusions of the discussions in the breakout groups as well as in the plenary were captured on a screen. These notes formed the basis of this final report of the workshop.

A draft of the report was prepared on 10 and 11 September 2015 by Bernadette Ossendorp and Hermine Reich and was reviewed by Raj Bhula. This draft was distributed to JMPR and the participants of the scientific workshop for an approximate two week commenting period (until 30 September 2015), with the aim of improving the final wording of the report. The workshop agree that comments relating to changes in the final recommendations and conclusions would not be accepted.

The final report of the workshop will be an EFSA event report of the meeting co-sponsored by FAO and WHO. Publication of the report is expected at the end of 2015, following clearance processes of FAO/WHO and in accordance with EFSA procedures.

In the next chapter each of the questions in the background document will be addressed individually, followed by the agreed list of conclusions and recommendations, a list of future work, and a roadmap regarding the follow-up of the workshop.

Some participants were of the opinion that the approach of discussing the individual parameters of the IESTI equation in isolation, without considering the modifications of other parameters at the same time would not allow for a comprehensive understanding of the expected impacts and outputs of the modified equations. However, there was good agreement that each individual parameter should have a scientifically robust basis. When these parameters are combined with the appropriate algorithm, the outcome of the exposure assessment would be a reliable indicator of the short-term exposure. Thus, it was agreed to follow the approach proposed in the agenda and discuss the questions raised in the background document.

The scope of the IESTI methodology was put up for discussion in the stakeholder meeting, where it was recognized that the purpose of the assessment could be either one of two options:

- evaluation of the dietary risk related to a specific use or

- ·evaluation of the dietary risk related to a specific MRL.

In the stakeholder meeting, this issue could not be settled, but with reference both to the Codex Committee on Pesticide Residues (CCP R) and EU legislation (FAO/WHO, 2005; Regulation (EC) No 396/2005[2]), most of the participants in the workshop were of the opinion that the IESTI methodology should address the second bullet poi nt, thu s the regulatory question about whether the dietary exposure related to a specific MRL is 'safe', in the sense that a residue present at the level of the MRL should not lead to an exposure exceeding the ARfD.

3. Detailed discussions

3.1. Replacing the HR/STMR in the IESTI equations with the MRL

Q1: Is it appropriate t o replace the HR and STMR by the MRL in all cases (case 1, 2a/2b and 3) of the IESTI equation?

- Yes, it is appropriate, provided that other parameters of the IESTI equation are also considered (see question 21).

It was recognized that the HR was originally chosen as a starting point in the dietary risk assessment because it reflects a residue closely related to the MRL but defined according to the residue definition for dietary risk assessment (i.e. includ ing all relevant metabolites) instead of the residue definition for enforcement (which comprises only the marker substance(s)). In addition, the HR relates to the edible portion, whereas the MRL relates to the raw agricultural commodity. However, since the level of the MRL is the highest residue level in tre ated samples that can legally be put on the market , it was agreed that it will be more transparent and therefore easier to communicate to start the calculations with the value of the MRL. Of course, this value will need to be adjusted to match the residue definition for dietary risk assessment, and to relate to the edible portion.

It was also mentioned that the HR was selected in the past because it is a fixed value while the MRL would depend on the method used to derive it (e.g. statistical method or expert judgement); however this is no longer the case with the introduction of the OECD MRL calculator which provides a harmonised methodology for estimating MRLs.

Most of the arguments raised in the stakeholder meeting against the replacement of the HR with th e MRL (see Annex B, Summary of the Stakeholder Meeting) were not supported by the participants of the workshop.

For commodities that are currently assessed under case 3 of the IESTI equation , the po tential replacement of the STMR with the MRL was discussed under Q21.

3.2. Variability factor

Q2: Is it acceptable to work with one default variability factor for all compound/commodity combinations in case 2 equations or do you have data or arguments to substantiate the use of a deviating variability factor for cer tain commodities?

The experts were of the opinion that the question should be reworded to consider whether there is enough evidence that one variability factor can be used for all commodities (case 2 of the current IESTI equation). There was consensus that after considering the data assessed by JMPR (FAO, 2003, 2005) and by EFSA (EFSA, 2005), the answer to the question is yes.

It was noted that the impact of changing the variability factor should be evaluated in combination with a modification of other parameters.

Q3: Should the variability factor of choice be based on the average, median or another percentile distribution of the variability factors from the JMPR 2005 database?

[2] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

The variability factor should be based on the average as it is the best estimate for the deterministic methodology currently used, while taking into account the shape of the distribution of the data. Based on the available data the participants agreed to use a default variability factor of 3.

Q4: Should further research be recommende d to generate data allowing establishment of specific variability factors for certain compound/commodity combinations?

No, a huge dataset is already available. If the average value of the variability factor is used, new data are unlikely to change it substantially.

3.3. Conversion factors, processing factors

Q5: Is it appropriate that the IESTI is calculated using the residue level (dietary intake residue definition) that relates to residues present at the level of the MRL?

Yes, it is appropriate. However, the residue needs to be converted to match with the residue definition used for the dietary intake assessment.

Q6: If you agree with the Q5 proposal, would you prefer deriving a 'surrogate-MRL'[3] based on residue field trial data or would you prefer using a res idue definition conversion factor (CF_{RD})?

A preference was expressed for the use of conversion factors.

Very often the residue trials provided do not always contain values reflecting the residue definition for risk assessment although the regulation or registration system requires such data making it difficult to derive a reliable surrogate -MRL. The use of CF s is more practical although it includes uncertainties (e.g. if CF from metabolism studies does not exactly reflect the GAP and the practical conditio ns of use).

Q7: Is it appropriate to continue using a processing factor for peeling or processing to predict the residues in the raw edible portion or a processed commodity if only the residues for the raw agricultural commodity are available?

Yes, and it should continue to be substance/commodity specific.

It was noted that consumption data for processed products are not always available, limiting the use of processing factors.

Q8: Should the variability factor, conversion factor and the processing factor each be based on the median or another percentile of the distribution?

- The variability factor should be based on the average (see also Q3).
- The processing factors should be, in general, based on the median (see also OECD, 2008).
- The conversion factors should also be, in general based on the median.

3.4. Large portion

Q9: Should the P97.5 large portion value be derived from the distribution of consumption values of a dietary survey expressed as kg/kg bw, in order to express the large portion as kg/kg bw?

Yes (consensus view, it provides more precise results).

Q10: Do we need a harmonised list of the commodities for which large portions need to be derived (e.g. oranges raw and orange juice separately or total orange products?

Yes, robust consumption data are r equired for both processed and unprocessed products, but grouping of processed products is necessary to focus on those processed commodities important from an intake point of view and for which processing data are requested (OECD, 2008). This would better

[3] Surrogate MRL (as defined in the Background document, see Annex A): a high residue corresponding to the true MRL but relating to the residue definition for dietary risk assessment.

reflect the likely exposure of the individual and the types of processing practices covered by processing studies.

Q11: Would it be beneficial to have a harmonised large portion list for the whole world? If not, what would be the objections?

Yes, for JMPR it would be beneficial to have a globally harmonised list of large portions. It is noted that it is up to the risk assessor to use the full list or a subset, depending on the purpose of the risk assessment (global, regional or national).

3.5. Unit weight

Q12: Could the unit weight be removed from the IESTI equation, resulting in one case 2 equation?

Yes, because of the lack of reliability and comparability of the available data. In addition, other parameters of the IESTI equation should also be taken into account. By removing the unit weight, it is likely that conservatism will increase in certain cases, therefore it was agreed that this change can only be implemented if simultaneously the default variability factor of 3 will be agreed.

It was noted that the unit weight might still be needed to decide whether to use a variability factor, i.e. whether a particular commodity fits in Case 1 or the new Case 2. (See Q14).

Q13: If Q12 is not agreed, how should the LP_{person} be calculated?

The question is not relevant, since the participants agreed on Q12 above.

3.6. Options for new IESTI equations

Q14: Would you prefer option 1, 2 or 3 over the current IESTI equations?

Option 3 as described in the background document (Annex A, page 30) was preferred by almost all of the experts.

Replacing case 1 and case 3 of the current IESTI equation:

$$IESTI = LP_{bw} \times MRL \times CF \times PF$$

Replacing case 2a and case 2b of the current IESTI equation:

$$IESTI = LP_{bw} \times MRL \times v \times CF \times PF$$

A clear list of commodities for which the variability factor is not applicable needs to be defined. The list should preferably not be based on the unit weight since this is a variable parameter that is very hard to harmonise and implement. There might be the need of re-classification of small commodities (i.e. apricots). Meanwhile, the variability factor of 3 should be used for commodities for which the sampling protocols (as defined by OECD (2009), Codex (CAC, 1999) include a specification for a number of units to be sampled.

Specific discussions on case 3 of the current IESTI equation see Q21.

Q15: Are there other options that could be considered?

No further options were proposed.

3.7. Short-term exposure assessment for cases with residues below the LOQ

Q16: Should the LOQ be used in the IESTI equation in case the MRL is set at the LOQ for both situations (STMR=HR=MRL=LOQ and STMR=HR=0 & MRL=LOQ)?

The LOQ should be used as a default in a first tier estimate. Further considerations can then be made by the risk assessor to recommend use of a different value (e.g. if there is a confirmed 'no-residue

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situation'). Another option available to the risk manager may be to require more sensitive analytical methods

Q17: Is a variability factor, conversion factor and/or processing factor appropriate in case the residues of all composite samples lie at or below the LOQ?

Yes for the variability factor and processing factor. It was noted that conversion factors cannot be derived for LOQ values.

3.8. Short-term exposure assessment for animal products

Q18: How could an IESTI calculation based on the MRL be performed if the MRL is set for meat?

There is no need to change the current approach. If the MRL is set for muscle and fat separately, these values can be used in the IESTI equation assuming a 80/20 muscle/fat ratio (mammalian meat) and 90/10 muscle/fat ratio (poultry meat). If the MRL is set for meat (based on muscle residues for non-fat soluble pesticides and based on fat residues in case of fat soluble pesticides), the MRL could be used in the IESTI equation and as such would not take into account the muscle/fat ratio. However, the participants pointed out that the dietary intake estimate for meat hardly ever leads to an exceedance of the ARfD.

3.9. Level of protection

Q19: Is the number of MRLs that would pass the dietary risk assessment in the new versus the old methodology providing some confidence that the level of protection (LoP) has not changed drastically, in other words is the number a reasonable measure for the change in LoP?

No, the number of MRLs passing the dietary risk assessment using the new methodology is not a good measure for the change in LoP (as defined by EFSA).

It should be noted that participants disagreed on the definition of LoP and questioned whether it was needed at this stage. To assess it according to the definition of EFSA would be very resource intensive and demanding. Furthermore defining a LoP was considered as a risk management issue and therefore not of immediate relevance to this workshop.

Q20: Do you have other suggestions for estimating the change in LoP?

Although the number of MRLs passing the risk assessment is not a good measure for the change in LoP (see previous question) it might be of interest for risk managers to assess the potential consequences of such a change and to facilitate communication at implementation of the revised methodology. Also the ratio of intake estimates according to the different methodologies might be of interest for risk managers.

3.10. Impact on MRLs

Q21: Replacing STMR by MRL in case 3 commodities (cereals, tea, fruit juices) has quite an impact on the number of MRLs for these commodities. Would it be appropriate to reconsider the MRL setting process for these commodities?

The workshop agreed that there is no need to change the MRL setting process for processed commodities. However for commodities that are included in case 3, the MRL should be used in the IESTI equation for risk assessment always in combination with the appropriate processing factor. In relation to bulking and blending, participants agreed that there are substantial uncertainties and inconsistencies about the degrees of bulking and blending, which would not facilitate a harmonised approach. However, if the ARfD is exceeded, validated information on bulking and blending for processed products can be taken into account if it can be demonstrated that such bulking and blending is guaranteed to occur. The workshop also recommended further investigation of the bulking and blending practices.

The same principle would apply for milk. The MRL should be used in the first instance, and processing factors for dairy products could be used if available.

Using the MRL for risk assessment would solve the problems encountered in enforcement practice s (critical situation: the STMR is safe but the MRL or even residues below the MRL would lead to an exceedance of the ARfD).

See also Q10 regarding the need of consumption data for processed commodities.

Q22: Should additional data be checked during the pilot period?

The experts recommended not to undertake a pilot project using the current and the new methodology in parallel. A s indicated in the stakeholder meeting, decision making and risk communication would be difficult if two different estimates are provided to risk managers.

A retrospective analysis with existing data could be performed to explore the impact of the agreed changes for risk managers . It was noted that although most of the proposed changes could be implemented immediately, the availability of large portion data based on kg body weight would require further work.

However, as mentioned before, t he number of MRLs passing the risk assessment and the ratio of intake estimates according to the different methodologies might be of interest for international/regional/national risk managers to assess the potential consequences and to facilitate risk communication at implementation of the revised equation.

Q23: Should specific additional data be generated during the pilot period?

No, as it was recommended not to conduct a pilot study. See also previous question.

3.11. Use of IESTI equations for food inspection services

Q24: Is it acceptable that food safety inspection services use the IESTI equations and/or 'Threshold MRL' or 'Critical Commodity Pesticide Concentrations' for assessment of the safety of a single lot, using the concentration of the residue measured in the sample?

Yes, it was agreed that food inspection services should use the same equation, although it was noted that risk assessments would be performed depending on the discretion granted under the relevant legislation. It was suggested that the 'threshold MRL', a non -formal health based guidance level , which refers to the estimated residue concentration that would lead to an intake at the ARfD, was a domestic EU issue and should not be further discussed at the meeting.

Q25: Is it acceptabl e that food safety inspection services use the same variability, conversion and processing factors as used for authorisation of use and MRL setting?

Yes, if the IESTI equations are used for enforcement, the parameters should be the same as for MRL setting (LP, CF, VF, and PF) in order to avoid discrepancies in the two risk assessments. Instead of the MRL the residue concentration measured in the sample should be used. The participants felt that there is no need to use different variability factors for mark et samples given the small difference in mean VFs derived from supervised field trials and market samples and the overall uncertainties.

If private parties (e.g. retailers) perform short -term dietary risk assessments, they could also use the IESTI equation.

Q26: Would it be acceptable for food safety inspection services to use a lower large portion from the national food survey instead of the higher globally harmonised large portion?

Yes, provided that the most critical large portion for the common marke t to which the risk assessment applies is selected.

Q27: Can we agree that lists of harmonised input parameters (LP, V F, PF, CF, Threshold MRLs) should be established and be made available for both authorisation and enforcement purposes?

Yes, however, it was noted that the threshold MRL is not an input parameter. Likewise, the variability factor would not differ from the default, noting that a list of commodities for which a variability factor (VF) is not necessary may need to be defined.

Q28: Could Code x (FAO/WHO) be the body responsible for gathering the input parameters?

As regards the large portions, yes (see Q11).

For the remaining input parameters, t here was no agreement on the added value of a global database, given the different residue definiti ons, processing factors and conversion factors. However, it is of utmost importance that lists of harmonised input parameters are made publicly available at regional/national level by the risk assessors . It was recommended that the design of any regional/national databases containing the information need to be aligned.

Q29: What would be an appropriate time schedule to update or re -evaluate such a database?

Countries should submit new data on LP to WHO GEMS/Food once available without waiting for a call for data. CF and PF data should be taken up in the regional/national database at the time when the evaluation of a compound at regional /national level is completed. For the VF no update was considered necessary since it is based on sufficiently large datasets, i.e. they will be fixed.

Q30: What would be the procedure if different residue definitions, PF and/or CF are derived between Codex and other regulatory bodies in the world, e.g. due to different policies or due to different use patterns?

Where global harmonisation cannot be achieved, national/regional legislation prevails.

In general, it was agreed that international discussion platforms for harmonising risk assessment approaches (not only for assessment of individual substances) are needed, such as t he current meeting. It was indicated that related activities are taken up by OECD (Joint review programmes , development of guidelines and guidance documents), though OECD has not covered the dietary risk assessment part yet.

4. Conclusions and recommendations

The primary aim of the meeting was to harmonize the methodology by addressing the individual parameters based on current knowledge, arguments and uncertainties. The recommended amendment to the IESTI equation is based on 15 years of experience in using th e current equations and the best available science. A 'roadmap' for implementing the new IESTI is needed, including the timeframe by when the required data need to be made available to the public.

The change in level of conservatism introduced by the revi sed IESTI equations was not assessed by the meeting, although examples were provided in the background document.

The participants of the Scientific Meeting derive d a range of recommendation s for further consideration of risk assessment and risk management bodies. The participants felt that implementation in 2016/2017 would be feasible.

Options for new IESTI equation

The meeting agreed that option 3 (as described in the background document on page 20) is the most appropriate:

New IESTI equation replacing case 1 and case 3 of the current IESTI equation:

$$IESTI = LP_{bw} \times MRL \times CF \times PF$$

New IESTI equation replacing case 2a and case 2b of the current IESTI equation:

$$IESTI = LP_{bw} \times MRL \times \nu \times CF \times PF$$

Input parameters (variability factor, processing factor and conversion factor) s hould be the same for both MRL setting and enforcement.

Replacing the HR/STMR with the MRL

It is appropriate to replace the HR and STMR by the MRL in all cases of the IESTI equation for MRL setting.

Variability factor

When it is appropriate to use a variability factor, then a default variability factor based on the average of a sufficiently large dataset should be used for all commodity/pesticide combinations. Based on the available data the participants agreed to use a default variability factor of 3 (FAO, 2003, EFSA 2005.

A clear list of commodities for which the variability factor is not applicable when calculating short-term dietary intakes, needs to be defined.

Meanwhile, the IESTI equation, including a variability factor, is applicable if the sampling protocols (as defined by OECD and CODEX) include a number of units to be sampled.

Conversion factors and processing factors

The use of a conversion factor for risk assessment is preferred over the use of a surrogate MRL.

The conversion factors and processing factors should, in general, be based on the median values of available data.

Further guidance on the derivation of conversion factors is needed (the meeting is aware that guidance currently developed by OECD may address this issue).

Conversion factors and processing factors should be made publically available by the risk assessors in a database. If different databases are developed and made available by different risk assessors, the design/format of the databases should be agreed.

Large portion

The P97.5 large portion value should be derived from the distribution of consumption values of dietary surveys expressed as g/kg body weight.

A harmonized and comprehensive list should be developed, which should include all commodities and certain pre-defined processed commodities for which large portion data need to be derived.

A harmonized list or database compiling the large portions for the different diets should be developed at the global level, but risk assessors should be able to select different large portion values relevant to the country and/or common market they are addressing. Data included in this database should comply with agreed quality criteria.

Further guidance on how to derive a large portion value is required (e.g. the minimum numbers of eating events that would give a reliable estimate, how to fill in the gaps (extrapolation?) etc).

Unit weight

The meeting agreed that the unit weight parameter can be removed from the IESTI equations.

Residues below LOQ

Where the MRL is set at the LOQ, the LOQ should be used by default in the IESTI equation.

Where the use of the LOQ in the IESTI equation leads to an exceedance of the ARfD and clear evidence of a no-residue situation is provided, further consideration by risk assessors and/or risk managers is possible.

Exposure assessments for animal commodities

For assessing commodities of animal origin, the HR/STMR will be replaced by the MRL, as for plant commodities.

Impact on intake estimates

The number of MRLs passing the risk assessment and the ratio of intake estimates according to the different methodologies might be of interest for risk managers to assess potential consequences and to facilitate risk communication at implementation.

Other issues raised

The Workshop only considered the IESTI equation and conclusions of this workshop cannot be transferred for multi-commodity or cumulative risk assessments. The conclusions would be applicable to both MRL setting for individual commodities and enforcement purposes.

In general, it was agreed that international discussion platforms for harmonising risk assessment approaches (not only for assessment of individual substances) are needed, such as the current meeting. It was indicated that related activities are taken up by OECD (Joint review programmes, development of guidelines and guidance documents), though OECD has not covered the dietary risk assessment part yet.

Data required for implementation of the revised IESTI equations

Large portions based on individual body weight need to be derived to replace the large portions based on kg per person.

Recommended Future work required to refine the risk assessment

- A clear list of commodities for which the variability factor is not applicable needs to be developed.
- Information on bulking and blending practices needs to be gathered.
- Further guidance on the derivation of conversion factors is needed (the meeting is aware that guidance currently developed by OECD might address this issue).
- Conversion factors and processing factors should be made publically available by the risk assessors in a database. If different databases are made available by different risk assessors, the design of the databases should be agreed
- A harmonized and comprehensive list of commodities and certain pre-defined processed commodities for which large portion data need to be derived should be developed. Processing studies should be conducted by addressing the commodities that are identified in the harmonised list.
- A harmonized list or database compiling the large portions for the different diets should be developed at global level . Data included in this database should comply with agreed quality criteria.
- Further guidance on how to derive a large portion is required.

Roadmap

The final report of the workshop will be an EFSA event report of the meeting co-sponsored by FAO and WHO. The aim for publication is by the end of 2015. Upon publication, the report will be made available on the EFSA website.

The draft report will be provided to JMPR 2015 meeting (10 to 24 September 2015) , for its consideration.

The report and the conclusions of JMPR may be on the agenda of CCPR 2016 (25 to 30 April 2016). It is recommended to organise a side event in the framework of this CCPR meeting , where CCPR members will be informed on the proposed amendment of the IESTI equations.

The outcome of the workshop will actively be shared with regional/national risk assessment and risk management bodies as well as with the participants of the stakeholder meeting. EFSA intends to further facilitate international discussions among all stakeholders and disseminate information as part of the next steps towards implementation of the revised methodology. Regional and national risk management authorities are encouraged to follow.

Further strategies on the implementation of the revised IESTI equations will be developed following the discussions with risk management bodies, and the definition of the responsible bodies.

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Abbreviations

ARfD	Acute Reference Dose
bw	Body weight
CV	Conversion factor
FAO	Food and Agriculture Organisation of the United Nations
HR	Highest residue
IESTI	International Estimate of Short-Term Intake
LoP	Level of Protection
LOQ	Limit of quantification
LP	Large portion
MRL	Maximum Residue Level
PF	Processing factor
RAC	Raw agricultural commodity
STMR	Supervised trials median residue
VF	Variability factor
WHO	World Health Organization

Appendix A – Organizing Committee

Bernadette Ossendorp, Head of RIVM department for Food Safety , Chair of the EFSA/PPR Panel 2012 to 2015, Coordinator of WHO Collaborating Centre of Chemical Food Safety at RIVM

Luc Mohimont, European Food Safety Authority, Pesticides Unit

Hermine Reich, European Food Safety Authority, Pesticides Unit

Davide Arcella, European Food Safety Authority, Pesticides Unit

Yong Zhen Yang, FAO Plant Production and Protection Division (AGO), FAO Joint Secretary to JMPR

Philippe Verger, WHO Department of Food Safety and Zoonoses, WHO Joint Secretary to JMPR

Appendix B – List of participants of scientific workshop

8/9 September 2015

An open call for expression of interest to participate in the scientific workshop was published in May 2015 on the EFSA website. Participation in the workshop was limited to invited experts acting in their personal capacity and selected by EFSA, FAO and WHO based on expertise in dietary exposure assessment of pesticide residues, representation from different geographic and economic regions, gender balance, declaration of interests and diversity of experience and scientific backgrounds. Deadline for submitting the nomination was 19 June 2015.

The following experts admitted to the Scientific Workshop within the deadline and w ere invited to participate.

Last name	First name	Affiliation	Country
AMBRUS	Árpád	JMPR	HUN
ARCELLA	Davide	EFSA	
BHULA	Raj	APVMA	AUS
BOGOEVA	Irena	Risk Assessment Centre, Bulgarian Food Safety Agency	BGR
BREYSSE	Nicolas	ANSES	FRA
CALDAS	Eloisa	University of Brasilia	BRA
DOHERTY	Michael	U.S. EPA - OPP - HED	USA
DUJARDIN	Bruno	EFSA	
FRIEL	Anja	EFSA	
GOMEZ RUIZ	Jose Angel	EFSA	
HAMEY	Paul	Health and Safety Executive	GBR
HOHGARDT	Karsten	Federal Office of Consumer Protection and Food Safety (BVL)	DEU
JARRAH	Samira	EFSA	
JENSEN	Bodil Hamborg	Technical University of Denmark	DNK
KOMADA	Mitsuko	The Norwegian Food Safety Authority	NOR
MACLACHLAN	Dugald	Department of Agriculture/JMPR	AUS
MAHIEU	Karin	National Institute for Public Health (RIVM)	NLD
MICHALSKI	Britta	Federal Institute for Risk Assessment (BfR)	DEU
MIRON	Ileana	EFSA	
MOHIMONT	Luc	EFSA	
MORA-GUZMÁN	Amanda	Instituto Nacional de Salud	COL
MOSBACH-SCHULZ	Olaf	EFSA	

Last name	First name	Affiliation	Country
NOORBAKHSH	Roya	ISIRI-SRI	IRN
OSSENDORP	Bernadette	WHO Collaborating Centre on Chemical Food Safety, RIVM	NLD
PIRES	Marcus	Brazilian Health Surveillance Agency	BRA
QIAO	Xiongwu	Shanxi Academy of Agricultural Sciences	CHN
REICH	Hermine	EFSA	
RIETVELD	Anton	National Institute for Public Health (RIVM)	NLD
SAIKAEW	Panpilad	National Bureau of Agricultural Commodity and Food Standards	THA
SIEKE	Christian	BfR representing JMPR FAO Group	DEU
SPUNGEN	Judith	U.S. FDA/Center for Food Safety and Applied Nutrition	USA
VAN DER SCHEE	Henk	Netherlands Food and Consumer Products Safety Authority	NLD
VAN DER VELDE-KOERTS	Trijntje	National Institute for Public Health (RIVM) / JMPR	NLD
VERGER	Philippe	World Health Organization (WHO)	
VIAL	Gaelle	ANSES	FRA
YAMADA	Yukiko	JMPR	JPN
YANG	Yong Zhen	Food and Agricultural Organization (FAO)	
YAU	Chung Wan Joan	Centre for Food Safety, Food and Environmental Hygiene Department	HKG
ZARN	Jürg	JMPR	CHE

Appendix C – Declarations of interest

Public hearings of EFSA are normally organised without requesting the participants to submit a declaration of interest. It was however decided in this case to request such a declaration of interest because this event is a self -standing event and not a preparatory step for a subsequent activity of EFSA.

The report of the workshop organised by EFSA and co -sponsored by FAO and WHO will be an output of EFSA intended to be the basis of a decision to be taken at international level on the appropriateness to revise the IESTI equation. Therefore, all participants to this event who are not staff of the co -sponsoring bodies (EFSA, F AO and WHO) have been invited to submit their ADOIs, after having been informed of the EFSA policy (E xecutive Director decision on declaration of interests[4]). The declarations, and eventual additional information available in the registration forms, were s creened by EFSA following the criteria of article 8.2 of the ED decision on Declarations of Interests and the summary presented to FAO and WHO as co -sponsoring organisations for their assessments.

The participation of experts fully familiar with acute expo sure assessments and the current equation was considered essential for this scientific workshop. As expected, it results from this screening that the vast majority of the participants present a conflicting interest resulting from their membership of JMPR or national committees using the IESTI equation or from their employment by an organisation responsible for risk assessment or risk management on the basis of the IESTI equation (classified as activity III and/or IV according to the EFSA categorization). Th e interests can be perceived as of a nature to restrict the capacity of these experts to act totally independently as any proposal to revisit the IESTI equation may impact the earlier RA or RM activities conducted with the current equation.

However, all th e conflicts of interest identified were related to Food Safety Organisations as defined by the EFSA independence policy and did not prevent the participation of the experts in the role of member of a scientific expert group.

Bernadette Ossendorp was chairing the Scientific Workshop in her capacity of coordinator of the WHO collaborating centre on chemical food safety in RIVM, one of the co -sponsoring bodies of the workshop.

Workshop participants were requested to indicate orally additional interests at the beginning of the workshop. No additional interests were declared.

[4] Available at: http://www.efsa.europa.eu/sites/default/files/assets/independencerules2014.pdf

Appendix D – Approved agenda for scientific workshop

EFSA Scientific Workshop, co-sponsored by FAO and WHO

Revisiting the International Estimate of Short-Term Intake (IESTI equations) used to estimate the acute exposure to pesticide residues via food

8-9 September 2015 | WHO (Geneva, Switzerland)

Agenda

Overall Chair: Bernadette Ossendorp, Coordinator of the WHO Collaborating Centre on Chemical Food Safety, RIVM (NL)

Co-chairs: Philippe Verger, WHO
Luc Mohimont, EFSA

Day 1 – Tuesday, 8 September 2015		
8.30-9.00	Registration	
9:00-9:30	SESSION 1: Introduction (Salle B)	
9:00-9:10	Welcome and opening Bernadette Ossendorp, Coordinator of the WHO Collaborating Centre on Chemical Food Safety, RIVM (NL)	
9:10-9:20	Welcome address Kazuaki Miyagishima, M.D. Director, Department of Food Safety and Zoonoses Health Security and Environment, WHO Luc Mohimont, Deputy Head of Unit, Pesticides Unit, EFSA	
9:20-9:25	Adoption of the agenda	
9:25-9:30	Declarations of interest	
9:30-16:30	SESSION 2: Discussion in breakout groups (Salle B)	
9:30-10:00	Brief introduction and purpose of the meeting Introduction to programme for breakout groups	
10:00-10:30	Coffee break	
10:30-12:30	Breakout group A (Salle B) Discussion of questions raised in the background document (Q1 to Q18)	Breakout group B (Salle C) Discussion of questions raised in the background document (Q19 to Q30)
12:30-14:00	Lunch (Canteen)	
14:00-15:30	Breakout group A (Salle B) Continue discussion of background document (Q19 to Q30) and questions put forward by Stakeholder Meeting	Breakout group B (Salle C) Continue discussion of background document (Q1 to Q18) and questions put forward by Stakeholder Meeting
15:30-16:00	Coffee break	
16:00-16:30	Preparation of summary report of Breakout group A	Preparation of summary report of breakout group B
16:30-18:00	SESSION 3: Plenary discussion (Salle B)	

16:30-17:30	Report back from breakout groups to plenary (30 min per group)
17:00 - 18:00	Questions and answer session
20:00 Networking dinner (Le Point du Jour)	

Day 2 – Wednesday, 9 September 2015	
9:00-14:45	SESSION 4: Plenary discussion (Salle B)
9:00-9:10	Introduction to day 2
9:10-10:30	Drafting of recommendations and conclusions on issues raised in background document and during Stakeholder Meeting Replacing the HR/STMR with the MRL Variability factor Conversion factors and processing factors
10:30-11:00	Coffee break
11:00-12:30	Continue: Drafting of recommendations and conclusions Large portion Unit weight Options for new IESTI equations Residues below LOQ Exposure assessments for animal commodities
12:30-13:30	Lunch (Canteen)
13:30-14:20	Continue: Drafting of recommendations and conclusions Impact of changing IESTI equations on level of protection Impact on MRLs Acute exposure assessments for food safety inspection services Other proposals raised during stakeholder meeting and previous discussions
14:20-14:30	Any other topics
14:30-14:45	Coffee break
14:45-16:00	SESSION 5: Plenary discussion (Salle B)
14:45-15:45	Adoption of key conclusion and recommendations
15:45-16:00	Closing of the Scientific Workshop

Annex A – Background document

On 29 July 2015, all participants to the Stakeholder Meeting and Scientific Workshop on Revisiting the International Estimate of Short -Term Intake (IESTI) received the so -called 'Background document' describing the issues to be discussed and proposals for possible ways forward (see Section 1 of the event report, page 6).

Compared to the original version circulated to the participants of the Stakeholder Meeting and the Scientific Workshop, the version of the Background document presented in this document contains the following editorial changes:

1. The questions at the end of the sections 2 to 4 (and the respective subsections) were numbered (Q1 to Q30)
2. Page 8: at the end of the second paragraph the text reading 'P95 residue in units / P50 residue in units' was corrected to 'P97.5 residue in units / mean residue in units'.
3. Page 19, the term CFRD was corrected to CF_{RD}.
4. Page 38, Appendix 2: A header was added to the Figure, and the arrows were moved to the left
5. Page 39, Appendix 2: the term PFENF was corrected to PF_{ENF}, and the term PFRISK to PF_{RISK}
6. Throughout the document a consequent use of the term 'raw edible portion' was implemented.

Revisiting the IESTI equation(s)

WHO - Collaborating Centre on Chemical Food Safety
RIVM (Dutch National Institute for Public Health and the Environment)[1]

Authors:
Trijntje van der Velde-Koerts
Anton Rietveld
Karin Mahieu
Bernadette Ossendorp

[1] http://www.rivm.nl/en/Topics/W/WHO_Collaborating_Centre_on_Chemical_Food_Safety
email: whocc.cfs@rivm.nl

Preface

In September 2015, EFSA, FAO and WHO will jointly host a Stakeholder Meeting and a Scientific Workshop to revisit the International Estimate of Short -Term Intake (IESTI). The main objectives of the scientific workshop are to evaluate the parameters within the IESTI equations as well as the equations themselves in order to propose ways to improve the methodology.

The WHO Collaborating Centre on Chemical Food Safety at the Dutch National Institute for Public Health and the Environment (Dutch acronym: RIVM) h as prepared this Background document for the event. The authors are greatly in debt to a number of peer-reviewers who have significantly improved the document by providing constructive comments on a very tight schedule. A first draft was circulated for com ments among the members of the Organizing Committee. A revised draft was again circulated to the Organizing committee and in addition to a number of external peer-reviewers.

The Organizing Committee:

Hermine Reich , EFSA Pesticides Unit, Head of MRL team, r esponsible for PRIMo (Pesticide Residue Intake Model)

Luc Mohimont, EFSA Pesticides Unit, Head of the team supporting the Panel on Plant Protection Products and their Residues (PPR Panel)

Davide Arcella , EFSA Evidence Management (DATA) Unit, oral exposure assessment expert

Yong Zhen Yang , FAO Plant Production and Protection Division (AGP), FAO Joint Secretary to JMPR

Philippe Verger, WHO Department of Food Safety and Zoonoses, WHO Joint Secretary to JMPR

Bernadette Ossendorp, Head of RIVM dept. for Food Sa fety, Chair of EFSA/PPR Panel 2012-2015, Coordinator of WHO Collaborating Centre on Chemical Food Safety at RIVM

The external peer-reviewers:

Eloisa Dutra Caldas, Pharmaceutical Sciences Department, College of Health Sciences, University of Brasilia, Brazil (JMPR/FAO Panel member & Rapporteur)

Peter Craig , Senior Lecturer in the Department of Mathematical Sciences, Durham University, UK

Michael Doherty, Office of Pesticide Programs, Health Effects Division, Risk Assessment Branch II, United States Environmental Protection Agency, Washington DC, USA (JMPR/FAO Panel Member)

Disclaimer: This document does not necessarily represent the view of EFSA. The present document has been conceived as a working document to provide the background information on the current methodology used to perform short-term dietary exposure estimates for pesticide residues in food and stimulate expert discussions during the stakeholder conference and the expert workshop 7 – 9 September 2015.

BACKGROUND DOCUMENT

EFSA/WHO/FAO Workshop 7-9 September 2015

Dugald MacLachlan , Australian Government Department of Agriculture, Canberra, Australia (Chairman of the FAO Panel of JMPR)

David Miller , Office of Pesticide Programs, Health Effects Division, Branch chief of Chemistry and Exposure Branch, United States Environmental Protection Agency, Washington DC, USA

The document is intended to provide background information before the event starts to participants to both the Stakeholder Meeting and the Workshop. In addition, the document identifies issues that need attention during the event. The Background document does not necessarily represent on all aspects the view of EFSA, FAO, WHO or any of the peer -reviewers. The document is not confidential and may freely be shared and discussed with colleagues in order to prepare for the event.

Following the event, a joint EFSA/FAO/WHO Technical Report will be prepared that will serve as a basis for discussion by JMPR, national/regional food safety authorities, and ultimately decision-makers on renewing the IESTI equations.

Table of Contents

1 Introduction

The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg) to be legally permitted in or on food commodities and animal feeds. MRLs are based on Good Agricultural Practice (GAP) data and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable (FAO, 2000).

Initially, the toxicological acceptability of the MRL was determined by estimating a life-time exposure to the residue and comparing this with the Acceptable Daily Intake (ADI). However, in the early 1990s, it became apparent that, in some cases, residues of a chemical could pose risks due to a single or a few days of exposure. Research on residues of acutely toxic pesticides (organophosphates and carbamates) in individual fruits and vegetables revealed random occurrences of comparatively high residue levels. Some individuals who consume significant amounts of such foods will occasionally eat the "hot" commodity unit (Hamey and Harris, 1999).

Acute dietary exposure assessments may be performed using deterministic (point values) or distributional (probabilistic) methodologies. At an international level, a deterministic methodology was developed to address the calculation of the acute dietary exposure to pesticides, the International Estimated Short Term Intake (IESTI) (For a chronological history of the acute RA methodology see [Hamilton & Crossley, 2004, WHO, 2009]).

At its 1999 meeting [JMPR, 1999], JMPR performed acute dietary exposure assessments for the first time. For pesticides with low acute toxicity, JMPR concluded that "an ARfD is unnecessary" and that assessing the acute exposure is irrelevant. In the IESTI method, the estimates are performed for each crop separately; as it is considered that it would be unlikely that an individual will consume, within a meal or 24 h, two large portions (LP) of different commodities that contain the same pesticide at the highest residue level. This methodology has been further refined by subsequent JMPR meetings, and the equations used by JMPR are shown in paragraph 1.1 of this paper[2].

It is important to note that the IESTI equations are designed for the purpose of MRL-setting (prospective dietary risk assessment), using residue data derived from supervised field trials conducted at the critical GAP (cGAP). Hence, the equations were not designed for calculating the actual exposure of a given population (retrospective dietary risk assessment), which depends on monitoring data. The Codex Committee on Pesticide Residues (CCPR) concluded that food containing residues at the level of the adopted Codex MRL must be safe for the consumers (CX/PR/05/37/4).

In other words, the acute exposure - MRL setting scenario should answer the question, whether the MRL allows for an appropriate level of protection for individuals eating a particular commodity with residues at the level of the MRL [EFSA 2009].

Codex Member States which use Codex MRLs, implicitly use the IESTI equations. In Australia and the EU, the IESTI equations are used to estimate the short term dietary

[2] First two paragraphs adapted from 'Principles and methods for the risk assessment of chemicals in food', EHC 240, 2009, Chapter 6

intake from pesticides for both authorisation of use and MRL setting. The IESTI equations are also used by national food safety inspection services (to decide whether food products analysed in national monitoring programmes can be considered safe for consumption. Although the same IESTI equations are used, the input parameters (residues, variability factors, unit weights, large portions) differ among international bodies (JMPR, EFSA) and individual countries. Because of differences in these input parameters, the outcome of acute risk assessments may differ for a single crop-pesticide combination in different parts of the world. The use of different input parameters creates trade barriers and concerns among the general public as to whether the MRL can be considered safe. Therefore, an evaluation of the IESTI calculation is proposed.

1.1 IESTI equations currently used for acute dietary exposure assessments

In this section the concept developed for calculating the IESTI is briefly described.

It should be noted that a pesticide residue is defined as the combination of the pesticide and its metabolites, derivatives and related compounds to which the MRL or STMR apply. In some instances two residue definitions are needed for one compound, because the residue definition for compliance with MRLs needs to be a simple residue definition suitable for practical routine monitoring and enforcement of the MRL, whereas the residue definition for dietary intake purposes should include metabolites and degradation products of toxicological concern irrespective of their source (FAO, 2002). The IESTI is designed to assess dietary intake on the basis of the the residue definition for dietary intake.

All users of the IESTI apply the following definitions and equations:

LP_{person} Highest large portion reported (97.5th percentile of consumers only), kg of food per person per day.

HR Highest residue in composite sample [3] of raw edible portion found in the supervised trials performed according to GAP used for estimating the maximum residue level (in mg/kg).

HR-P Highest residue in a processed [4] commodity, mg/kg, calculated by multiplying the highest residue in the raw commodity by the processing factor.

bw Mean body weight, kg, provided by the country from which the LP was reported. The bodyweight represents the mean body weight of the population group of the dietary survey from which the LP was derived (e.g. general population, adults, children).

U_e Unit weight of the raw edible portion, kg, provided by the country where the trials that gave the highest residue were carried out.

U_{RAC} Unit weight of the raw agricultural commodity (RAC), kg, provided by the country where the trials that gave the highest residue were carried out.

v Variability factor, the factor applied to the composite residue to estimate the residue level in a high-residue unit.

[3] Composite sample = samples composed of multiple units of the same commodity
[4] 'Processing' can either relate to removing inedible parts of a commodity, e.g. peeling a banana, or to further (industrial or household) preparation, e.g. milling of grain, cooking of spinach.

STMR Supervised trials median residue in the raw edible portion of a food commodity (expressed as mg/kg), derived from the same set of supervised field trials as the HR.

STMR-P Supervised trials median residue in processed commodity (in mg/kg).

Case 1

The residue in a composite sample (raw or processed) reflects the residue level in a portion of the commodity that would be consumed at one meal (whole fruit or vegetable unit weight (expressed as RAC) is below 0.025 kg). Case 1 also applies to meat, liver, kidney, edible offal and eggs, and for grains, oilseed and pulse s commodities when the estimates were based on post-harvest use of the pesticide.

$$\mathrm{IESTI} = \frac{\mathrm{LP_{person}} \times (\mathrm{HR\ or\ HR\text{-}P})}{\mathrm{bw}}$$

Case 2

The one meal portion, such as a single fruit or vegetable unit, might have a higher residue than the composite (whole fruit or vegetable unit weight (expressed as RAC) is equal or above 0.025 kg).

Case 2a

The unit weight (raw edible portion) of the commodity is lower than the large portion weight.

$$\mathrm{IESTI} = \frac{\{\mathrm{U_e} \times (\mathrm{HR\ or\ HR\text{-}P}) \times \mathrm{v}\} + \{(\mathrm{LP_{person}} - \mathrm{U_e}) \times (\mathrm{HR\ or\ HR\text{-}P})\}}{\mathrm{bw}}$$

The Case 2a formula is based on the assumption that the first unit contains residues at the [HR × *v*] level and the next ones contain residues at the HR level, which represen ts the residue in the composite from the same lot as the first one.

Case 2b

The unit weight (raw edible portion) of the commodity exceeds the large portion weight.

$$\mathrm{IESTI} = \frac{\mathrm{LP_{person}} \times (\mathrm{HR\ or\ HR\text{-}P}) \times \mathrm{v}}{\mathrm{bw}}$$

The Case 2b formula is based on th e assumption that there is only one consumed unit and it contains residues at the [HR × *v*] level.

Case 3

Case 3 is for those processed commod ities where, because of bulking or blending , the STMR-P represents the likely highest residue. Case 3 also applies to milk and to grains, oilseeds and pulses for which the estimates were based on pre -harvest use of the pesticide.

$$\text{IESTI} = \frac{\text{LP}_{\text{person}} \times (\text{STMR or STMR - P})}{\text{bw}}$$

The concept of variability fac tor was introduced to take into account the different concentrations of residues in individual portions of a composite sample and average residue concentration in the sam ple lot represented by the composite sample. The variability factor (*v*) was defined as the 97.5th percentil e of the residue concentrations present in commodity units (RAC) divided by the mean residue concentration of the sample population: P97.5 residue in units / mean residue in units.

In the IESTI methodology, the estimates are performed for each crop individually, as it is unlikely that an individual will consume, within a meal or 24 h, a large portion of more than one food containing the highest residue level (the one that incorporates the variability factor). The IESTI calculations can be performed separately to estimate dietary exposure from consumption of the unprocessed or processed form of a food commodity, when relevant.

2 Purpose of the workshop and topics to be discussed

Currently, JMPR and regulatory authorities use diverging input parameters (Table 1) in the IESTI equation, reflecting different regional cultural habits (parameter related to food consumption) and different assumptions (other parameters).

Table 1 Differences in applied input parameters in the IESTI equation

IESTI parameter	Difference, reasons for differences
unit weight (U_{RAC} and U_e)	Different unit weights between countries, EU and JMPR because of different cultural habits and trading practices, lack of guidance how to derive information on unit weight and how to define the unit (e.g. spinach)
large portion (LP)	Different large portions between countries, EU and JMPR because of different cultural habits, l ack of clear guidance how the LP data are derived from food surveys
variability factor (v)	JMPR: variability factor v= 1 for case 1 & 3 and v= 3 for case 2a & 2b EU: v=1 for case 1 & 3, v= 5 or 7 for case 2a & 2b, depending on the unit weight
residue (HR, HR-P, STMR, STMR-P)	Different residue values between national/regional authorities and JMPR, because of differences in the submitted data and/or differences in use (dose rate, PHI). Lack of transparency whether HR/HR -P/STMR/STMR-P used in risk assessm ents refers to raw edible portion or RAC

The present workshop aims to discuss the input parameters in the acute dietary risk assessment and to consider options for a renewed and better harmonised IESTI equation, while trying to ensure the same level of p rotection (see Chapter 3) compared to the cur rent IESTI equation . The outcome of this workshop will serve as a basis for discussion by JMPR, national/regional food safety authorities and ultimately decision makers. Discussions also need to address the appr opriate IESTI equation for use by national food safety inspection services on market samples.

The discussions should address the following topics:

Use of the IESTI equation for authorisation and MRL setting:

- Is it appropriate to use the MRL instead of the HR /STMR in the IESTI equation(s)?
- Which variability factor should be used in the IESTI equation(s)?
- When to apply conversion factor s[5] and processing factor s[4] in the IESTI equation(s)?
- One harmonized worldwide large portion per commodity?
- Applicability of the Unit weight concept?

[5] Conversion factors accounting for different residue definition for enforcement and risk assessment

- Options for (a) new IESTI equation(s).
- How to deal with situations where residues are <LOQ?
- How to deal with animal commodities?

To facilitate discussion on the above topics, it is essential to agree on a common language to describe how changes to the IESTI equation affect the level of protection of consumers. This important aspect is developed in section 3 of this document. The workshop should address:

Level of protection (LoP)

- How does changing the IESTI equation affect the level of protection that is provided by MRL setting?

Although the IESTI equation was originally meant for dietary risk assessment for MRL setting of pesticides, the IESTI is also used by food safety inspection services for risk assessment when a batch is found to contain a residue level that exceeds the MRL. The workshop should address:

- What is the appropriate IESTI equation(s) for food safety inspection services?

2.1 Is it appropriate to use the MRL instead of the HR/STMR in the IESTI equation(s)?

The highest residue (HR) and the Supervised Trials Median Residue (STMR) used in the IESTI calculation refer to the residue as defined by the residue definition for dietary risk assessment present in the raw edible portion of the crop, while the MRL refers to the residue definition for enforcement purposes related to the commodity in trade (see Appendix 1). It is noted that in the absence of a HR or STMR for the raw edible portion, the HR or STMR of the RAC is used in the dietary risk assessment, adding additional uncertainty. The HR and STMR are estimated from supervised trials that have been conducted according to critical GAP. The uncertainties in these values are mainly associated with the residue dataset available. The minimum data requirements vary from three trials for minor or specialty crops to a minimum of eight trials for major crops. When only limited residue data are available, and the distribution of the residue population is not known, the resulting MRL recommendation can be substantially higher than the HR and the STMR. There is a concern that conducting the assessment using the HR value instead of the MRL might not assure the safety of consumers, mainly when the MRL is much higher than the HR and the short-term exposure is close to 100 % of the ARfD [JMPR, 2006]. In addition, a number of MRLs were identified that allow residue levels resulting in short term dietary exposures - as calculated with IESTI - exceeding the acute reference dose (ARfD).

In such situations, food safety inspection services cannot act because the legal limit – MRL- is not exceeded although the dietary exposure is calculated to be above the ARfD.

This triggered the question whether the HR (and STMR) in the IESTI equation should be replaced by the MRL.

An additional argument to use the MRL instead of the HR is that the MRL is derived by means of statistical methodology which may be considered as a more robust value for dietary risk assessment than the HR which reflects a single event and not the distribution of residue concentrations expected in reality.

Finally, estimating IESTI from the MRL (the legal limit) may contribute significantly to building trust among the general public.

Questions to be answered:

- Q1: Is it appropriate to replace the HR and STMR by the MRL in all cases (case 1, 2a/b and 3) of the IESTI equation?

2.2 Which variability factor should be used in the IESTI equation(s)?

To obtain representative samples from supervised field trials several units of the RAC are taken from a treated plot (see Table V.1 in FAO 2009). For crops with a unit weight of >25 g twelve to twenty-four individual units are homogenized in a composite sample and subsequently analysed. However, consumers are exposed to residues in individual units and the residue in the individual unit may be much higher than the residue measured in the composite sample. The variability factor is the factor applied to the composite residue to estimate the residue level in a high -residue unit. The variability factor is defined as the residue level in the 97.5th percentile unit divided by the mean residue level for the lot (FAO 2009) . As such, it is an uncertainty factor that reflects the variability of residues in individual units.

OECD has harmonized the various statistical approaches to calculate the MRL that were in use by JMPR, EU and NAFTA. Nowadays the MRL is calculated using an Excel tool, the OECD MRL calculator [OECD, 2011]. This OECD MRL calculator calculates the MRL based on the residue values selected from supervised field trials conducted at cGAP. For not fully censored datasets, the OECD calculator uses three approaches to derive the MRL proposal (the maximum of three calculated results is put forward as the MRL proposal by the calculator):

- the highest residue is used as a "floor" to guarantee that the MRL proposal is always greater than or equal to the highest residue;
- the mean and the standard deviation values of the dataset are computed; the "mean + 4 standard deviation" value is evaluated as the base proposal (referred to as "Mean + 4 SD" method); and
- the "3 × Mean × CF" method (The correction factor CF is equal to 1 – ⅔ × fraction censored data in the dataset).

The OECD MRL calculator usually results in higher MRLs than the previous methods used by JMPR, EU and NAFTA. In the calculation various uncertainties are already taken into account:

1. field-to-field variability (climate, dose rate, equipment, formulations),

2. variability caused by crops (crop varieties, crop sizes, crop growth stages),
3. sample to sample variability, and
4. analytical measurement variability.

Since the MRL is a limit developed for enforcement and not for dietary risk assessment the within-sample variability (unit-to-unit variability) is not taken into account in this OECD MRL calculator. It may be assumed that the variability factor used in equations 2a/2b at the level of the HR, as described above, also applies to the level of the MRL to account for unit-to-unit variability in composite samples. Therefore discussions need to address the appropriate variability factor to use.

The 2002 JMPR [JMPR, 2002] used variability factors of 1, 3, 5, 7 or 10 for different types of commodities. The variability factor used for calculation of the acute exposure depends on the unit weight (U_{RAC}) and may be influenced by the characteristics of the commodity and the kind of application of the pesticide or pesticide formulation. In 2002, the highest residue in a single commodity unit derived from a composite field sample (treated crop) consisting of ≥ 90 commodity units was considered to represent the 97.5th percentile of the population in the sampled lot. This method was stated to overestimate the unit-to-unit variability in more than 90% of the cases, because the highest residue can be much higher than the 97.5th percentile [Hamilton et al., 2004]. Another concern was that the calculated unit-to-unit variability would not make sense if most of the single commodity units were non-detects. Therefore, the Advisory Committee on Crop Protection Chemistry of the International Union of Pure and Applied Chemistry (IUPAC) took another approach to estimate variability factors and selected only those pesticide/commodity combinations where 95% or higher of the individual units had detectable residues. Evaluation of a wide range of studies on unit-to-unit variability in composite samples derived from supervised field studies and from the market place, showed an average variability factor of 2.7 (range 1.5-7.2) involving approximately 8000 unit analyses for a number of pesticides over a range of crops. Based on these studies, the Advisory Committee on Crop Protection Chemistry of the IUPAC recommended that a default variability factor of 3 should be applied in the absence of more accurate information [Hamilton et al., 2004].

After discussing the work of IUPAC, the 2003 JMPR agreed to replace the default variability factors of 3, 5, 7 and 10 by a new default variability factor of 3 for all commodities, except for U_{RAC} < 25 g where no variability factor is used (a variability of factor of 1 in the calculation sheets) [JMPR, 2003].

The EC agreed with the recommended change of the variability factor on head cabbage and head lettuce [EU, 2003] [6], but expressed its reservation about a general change of the default variability factor to the Codex Committee on Pesticide Residues (CCPR) in 2004, pending internal evaluation of this change in the EU. This internal evaluation involved research by the EFSA PPR Panel on the variability factor and on the acute dietary intake assessment [EFSA 2005, EFSA 2007], see below. In 2006, CCPR welcomed JMPR work done on variability factors and at the same time acknowledged the position expressed by the Delegation of the EC that the JMPR should use a higher default

[6] Nowadays, in EFSA PRIMo a variability factor v=5 is used for head cabbage and head lettuce, since MS expressed their preference to perform more conservative assessments.

variability factor of 5 and that the EC was of the opinion that different varia bility factors might be applicable to different commodities, pesticides and application methods [CCPR 38, 2006]. From that time onwards, JMPR has used a default variability factor of 3 while the EU has continued to use the 'old' variability factors [7] [FAO 2 002], resulting in recurring disagreements on the safety of Codex MRLs between the EU and the other Codex Member States.

In March 2005, at the request of the European Commission, the EFSA PPR Panel [EFSA, 2005] published an opinion on a variability factor to be used for acute dietary intake assessment of pesticide residues in fruit and vegetables. Following the analysis of a large dataset of residue concentrations in single units, the Panel found that the average variability factor for supervised field tria ls was 2.8, while it was 3.6 for market place samples. Because the variability factor is itself variable, the PPR Panel suggested that the European Commission might wish to consider this when choosing an appropriate default value for use in dietary exposur e assessments. To assist in this, the PPR Panel provided tables presenting a range of statistics. For example, it is estimated that the variability factors for supervised trials will exceed the proposed default value of 3 in 34% of cases, whereas the previ ous default value of 7 for medium -sized food items will be exceeded in 0.2% of cases. Similarly, the variability factors for market surveys averaged 3.6, and will exceed 3 in about 65% of cases and 7 in about 1% of cases. However, the PPR Panel also noted that the assessment of acute risks from dietary exposure uses conservative assumptions for portion size and the residue concentration as well as the variability factor. It was recommended to further investigate t he combined effect of these conservative ass umptions on the overa ll level of consumer protection (EFSA 2005).

The 2005 JMPR [JMPR, 2005] reviewed the variability factor used in the calculation of short-term intake. Based on this review, involving the consideration of a data set of more than 22000 r esidue results, including data from the FAO/IAEA Joint Division, supervised field trials and EFSA, the 2005 JMPR reconfirmed that owing to the inevitable random nature of the variability factor derived from the combined uncertainty associated with sampling and analysis, the best estimate of the default variability factor is the mean of the variability factors derived from samples of various crops. The 2005 JMPR reconfirmed that a default variability factor of 3 should be applied for $U_{RAC} \geq 25$ g if no empirically derived variability factors are available.

The most recent proposal made by the European Commission [EFSA, 2007] is using a default variability factor of 3 instead of 5 and 7 , but at the same time also replace the HR in Case 1 and Case 2 equations by the MRL.

MRL-setting is based on residue concentrations derived from supervised field trials (all crop treated at cGAP). There is at present no consensus on what variability factor, if any, should be used with market place samples. This depends critically on the nature of the sampling and where in the production/delivery chain the sampling takes place. Since the EFSA PPR Panel [EFSA, 2005] found that the average variability factor for supervised field trials was 2.8, while it was 3.6 for market place samples, the Panel recommended considering the use of different default variability factors when doing exposure assessments on market place samples versus supervised field trials. The rationale was

[7] In the EU the variability factor of 10 that was recommended by JMPR in 2002 for leafy vegetables and for granular soil treatment are not used.

that if sampling of commodities in trade is effectively on produce from a single field/orchard, a variability factor based on field trial data would be correct. However, if sampling takes place after mixing of lots from diverse sources, one would in principle need a larger variability factor, perhaps even one much larger than would be obtained from the market data part of EFSA (2005). It should be noted that this would potentially lead to a more conservative outcome for enforcement. A residue concentration that was considered to be 'safe' during authorization / MRL-setting may be assessed to be 'unsafe' when found in a lot in trade. Therefore it seems preferable to use the same variability factor for authorisation and enforcement. This is discussed further in Chapter 4.

EFSA (2005) was not able to separate sampling variability from differences between compound/commodity combinations due to there being only a limited amount of data where the same compound/commodity combination was investigated more than once. The distributions for variability factors reported in EFSA (2005) reflected a combination of both. It was also not possible to distinguish whether variability was due to commodity differences or compound differences, again due to the limited range of combinations covered by trials. This is an argument for using the same value for all compound/commodity combinations, except for cases where specific arguments exist for a different value.

Questions to be answered:

- Q2: Is it acceptable to work with one default variability factor for all compound/commodity combinations in case 2 equations or do you have data or arguments to substantiate the use of a deviating variability factor for certain commodities?
- Q3: Should the variability factor of choice be based on the average, median or another percentile distribution of variability factors from the JMPR 2005 database?
- Q4: Should further research be recommended to generate data allowing establishment of specific variability factors for certain compound/ commodity combinations?

2.3 When to apply conversion factors and processing factors in the IESTI equation?

If it is considered appropriate to utilise residues at the level of MRL in estimating short-term exposure with an IESTI, the residue levels need to be adjusted to the corresponding levels for dietary intake calculation, i.e. the MRL may be based on levels of parent compound only while for dietary intake calculation the residue may be defined as parent plus some metabolites. Additional adaptations of the IESTI equation are required because the MRL is set for the raw agricultural commodity (RAC) while the dietary exposure needs to be estimated for the residues in the commodity as consumed (e.g. edible part of the raw commodity, fruit juice, cooked vegetables, polished cooked rice).

Adjustment to levels corresponding to the dietary intake residue definition can be accomplished in two ways.

1) Usually, supervised field trials provide a range of residues relevant for dietary intake assessment as well as the residue range used to set the MRL. This residue dataset can be used in the OECD MRL calculator to provide a 'surrogate -MRL', i.e. a high residue corresponding to the true MRL but relating to the residue definition for dietary risk assessment.

2) A residue definition conversion factor (CF_{RD}) could be added to the IESTI equation to convert the residue for enforcement into the residue for dietary risk assessment (Appendix 1). Currently this procedure is used within EU and the median conversion factor is taken. The mathematical formula for CF_{RD} = dietary risk residue / enforcement residue (in the same commodity).

Adjustment to the residue in the food as consumed can be accomplished by using a peeling factor or processing factor (PF). A PF could be added to the IESTI equation to predict the residue in the raw edible portion or specified processed commodity if only data for the raw agricultural commodity are available (Appendix 2). Currently this procedure is used OECD-wide for processed commodities and the median processing factor is taken. The mathematical formula for PF = residue in a specified peeled or processed commodity / residue in the RAC.

In summary, the MRL may need to be multiplied by a variability factor, a peeling/processing factor and, perhaps, a residue definition conversion factor. For each of these variables (v, PF, CF_{RD},) a choice has to be made whether the mean, median or another percentile in the distribution is the best option. This depends on whether the observed variation of each of these quantities is considered to be "meaningful". If it is, one should target a suitable percentile rather than the median. Currently the median is used for processing factors and conversion factors. In case a choice is made for mean these factors can be multiplied ($mean_v$ $mean_{PF}$ $mean_{CF\_RD}$). However, in case a choice is made for a median or a higher percentile (e.g. P95) multiplication of these factors is mathematically not correct. Multiplication of P95 values for v, PF and CF_{RD} will lead to a significant overestimation of uncertainties. To avoid this overestimation, the three different distribution profiles for v, PF and CF_{RD}, could be combined to get one overall multiplication factor (MF). The mathematical procedure to arrive at a single MF is further detailed in Appendix 3, in order to be able to address this at a later stage when consensus has been reached on how to make the adjustment to levels corresponding to the dietary intake residue definition.

Questions to be answered:

- Q5: Is it appropriate that the IESTI is calculated using the residue level (dietary intake residue definition) that relates to residues present at the level of the MRL?
- Q6: If you agree with the Q5 proposal, would you prefer deriving a 'surrogate - MRL (see above) based on residue field trial data or would you prefer using a residue definition conversion factor (CF_{RD})?
- Q7: Is it appropriate to continue using a processing factor for peeling or processing to predict the residues in the raw edible portion or a processed commodity if only the residues for the raw agricultural commodity are available?
- Q8: Should the variability factor, conversion factor and the processing factor each be based on the median or another percentile of the distribution?

2.4 One harmonised worldwide large portion per commodity?

Large portions can be derived from Food Consumption Surveys (FCS) in different ways. How best to do that is not within the remit of the current workshop (see Appendix 4).

The current case 1, 2a, 2b and 3 equations use a Large Portion as kg/person divided by the mean bodyweight (LP_{person}/bw) of the population group of the dietary survey from which the LP was derived (e.g. general population, adults, children). In this way it is not possible to take into account a possible correlation between the amount consumed and the body weight and, since it is expected that the larger portions (based on **kg/person)** are consumed by subjects representing body weights above the average, the use of an average bodyweight can be considered as a conservative assumption. This is especially true for children due to the high variability in body weight among individuals of different ages but within the same children group in the survey. The direct use of the P97.5 from a distribution based on **kg/kg bw/day** would provide a more precise estimate for large portion. In addition it is noted that a P97.5 value from a distribution based on **kg/kg bw/day** values corresponds to babies/toddlers or children who eat a lot relative to their bodyweight. This effect is most obvious in FCS performed among the general population including a wide range of ages.

The LP should be matched to the commodity to which the HR or STMR relates. In the case of commodities that are predominantly eaten as the fresh fruit or vegetable, the LP should relate to the raw agricultural commodity. However, when major portions of the commodity are eaten in a processed way (e.g. grains) and when information on the residue in the processed commodity is available, the LP should relate to the processed commodity (e.g. flour or bread). However in practice, some countries derive one single large portion to cover both the raw and processed forms of a certain commodity, while other countries report the large portions for specified raw and processed commodities. For example, LPs can be derived for orange raw and orange juice separately, or for total orange products consumed on a single day (including orange raw, orange juice and other orange products). Currently, there is no clear definition of the commodities for which large portions need to derived, leading to different interpretations.

Both EU and JMPR use as large portion for a certain commodity the most critical and robust of the values reported by the individual member states. However, since Codex has more member states than the EU, they may be working with different LP values for a given commodity.

The 97.5th percentile consumption among consumers only (LP) can be very unstable. So it may change a lot from survey to survey. Ideally, every time a new consumption survey is conducted its impact on the existing highest LP per commodity should be assessed. A decision to change the highest LP per commodity may have impact on MRLs that were assessed before. However, to reassess all existing MRLs for a given commodity every time the highest LP for that commodity changes, would be quite time and resource intensive. Therefore, the use of one most critical LP per commodity could be considered.

In addition, national food surveys usually do not cover minority populations within a nation, simply because they did not take part in the food survey. To also protect minority populations one single harmonised highest large portion for authorisation for use and MRL setting could be used.

The above could be addressed by creating a list of LP default values to be used for a set number of years and to be reviewed after that period. This would ensure a level playing field. The current workshop could discuss whether a LP defaults list should be developed.

Questions to be answered:

- Q9: Should the P97.5 large portion value be derived from the distribution of consumption values of a dietary survey expressed as kg/kg bw, in order to express the large portion as kg/kg bw?
- Q10: Do we need a harmonised list of the commodities for which large portions need to be derived (e.g oranges raw and orange juice separately or total orange products)?
- Q11: Would it be beneficial to have a harmonised large portion list for the whol e world? If not, what would be the objections?

2.5 Applicability of the Unit weight concept?

In the IESTI calculation, the unit weight value (U) affects the outcome of the IESTI equation in two ways. The U_e determines whether the LP will be composed by more than one crop unit (Case 2a) or will be a portion of the unit (Case 2b) and subsequently determines which IESTI formula is applicable. Furthermore, the U_{RAC} determines whether a variability factor is to be applied to the HR. According to JMPR procedures, no[8] variability factor is used if the U_{RAC} is smaller than 25 g and a variability factor of 3 is used if the U_{RAC} is 25 g or higher. According to EU procedures, a variability factor of 1 is used if the U_{RAC} is smaller than 25 g, a variability factor of 7 is used if the U_{RAC} is between 25 g and 250 g, and a variability factor of 5 is used if the U_{RAC} is higher than 250 g.

Several countries have provided unit weight data without specifying whether the U values provided represent s the median of units consumed in a country or a different estimation. Also, it is not clear in all cases whether that value refers to the whole commodity or to the raw edible portion (JMPR 2006). For some crops it is not so evident how the unit weight should be expressed (e.g. spinach as single leaves, as plants or as bunches; bananas as single fruit or a hand of seven fruits). This also applies to other crops (e.g. elderberries, grapes, Chinese cabbage, rucola, carrots, tomatoes, beetr oots). Thus, more guidance would be needed on how to derive unit weight data. Without a clear rationale different unit weights are used in different parts of the world for the same crop commodities. It is noted that several commodities exist in varieties t hat have very different unit weights, e.g. , cherry tomatoes versus flesh tomatoes. The use of different unit weights results in very different outcomes of the IESTI, even if the large portion and residue levels are the same [Van der Velde-Koerts, 2010], see Figure 1.

Furthermore, the unit weight in the case 2a formula suggests that only one unit in the composite samples has a higher residue than the average residue of that composite sample, which may not be correct. There could be a second or a third unit weight that also has a higher residue than the average residue of that composite sample.

[8] Please note that 'no variability factor' equals using a variability factor of 1

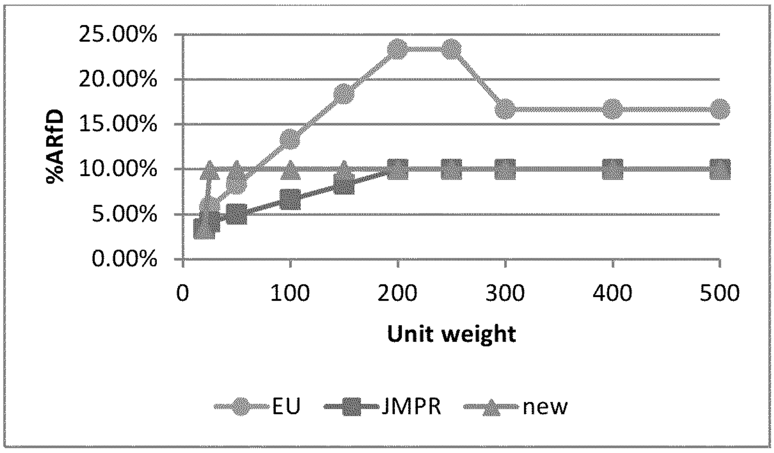

Figure 1 IESTI (expressed as %ARfD) as a function of unit weight ($U_{RAC}=U_e= 20-500$ g), while all the other parameters are kept constant (HR = 0.2 mg/kg, LP = 200 g/person, bw = 60 kg, ARfD = 0.02 mg/kg bw) for 3 situations: EU (current IESTI equation, v=1,5,7), JMPR (current IESTI equation, v=1, 3), new (new IESTI equation step 3, unit weight deleted, v = 1,3)

In the current IESTI equations, it is required to express the Large Portion (LP) as kg/person to compare the LP (97.5th percentile) with the unit weight to decide on the equation to be used (case 2a or case 2b) . Subsequently, in the current case 1, 2a, 2b and 3 equations the Large Portion as kg/person is divided by the average bodyweight (LP_{person}/bw). See Chapter 2.4 for the drawbacks on expressing the Large Portion (LP) as kg/person.

However, in case 2a the LP expressed as kg/person is required to calculate the exposure. So even in cases where the consumption distribution is based on kg/kg bw, this value has to be multiplied by the average bodyweight to get a kg/person value. This may result in an unrealistic high large portion, since the actual bodyweight can be much lower especially in surveys including large age differences ('general population surveys') . For case 1, case 2b and case 3 this is no problem, since the kg/person value is again divided by that same average bodyweight. But in case 2a only part of the unrealistic high large portion is multiplied by the variability factor, while the other part is not multiplied by the variability factor. This introduces additional errors in the exposure assessment.

Because of the substantial uncertainty in the values of the unit weight and the error that using the unit weight creates in the case 2a equation, it is proposed to delete the unit weight from the IESTI equations. This would imply an assumption that the whole LP contains a residue related to the level of the MRL multiplied by the variability factor. It is noted that this will not necessarily lead to a more conservative outcome depending on the outcome of the discussion on the proper variability factor(s) (see explanation above and Chapter 3.1,impact assessment)

Questions to be answered:

- Q12: Could the unit weight be removed from the IESTI equation, resulting in one case 2 equation?
- Q13: If Q12 is not agreed, how should the LP_{person} be calculated?

2.6 Options for (a) new IESTI equation(s)

Based on the discussion points given above the following options for new IESTI equations are proposed for discussion:

Option 1: keep equations as they are, but replace HR and STMR by MRL and use a conversion factor (CF_{RD}) to correct for difference in resid ue definitions (CF_{RD}) and use a peeling or processing factor (PF) to correct for residue differences in the RAC and peeled or processed product. Alternatively, instead of using MRL CF_{RD}, a 'surrogate-MRL[9]' can be derived from supervised field trials providing a range of residues relevant for dietary intake assessment.

Case 1 = case 3

$$IESTI = \frac{LP_{person} \times MRL \times CF \times PF}{bw}$$

Case 2a

$$IESTI = \frac{\{U_e \times MRL \times v \times CF \times PF\} + \{(LP_{person} - U_e) \times MRL \times CF \times PF\}}{bw}$$

Case 2b

$$IESTI = \frac{LP_{person} \times MRL \times v \times CF \times PF}{bw}$$

However, as discussed in para graph 2.4 and 2.5 , it could be considered to replace the LP_{person} by LP_{bw}.

Option 2: as option 1, but large portion based on distribution as kg/kg bw

Case 1 = case 3

$$IESTI = LP_{bw} \times MRL \times CF \times PF$$

Case 2a

$$IESTI = \frac{U_e \times MRL \times v \times CF \times PF + [(LP_{bw} \times bw) - U_e] \times MRL \times v \times CF \times PF}{bw}$$

Note that t he bodyweight represents the mean body weight of the population group of the dietary survey from which the LP was derived (e.g. general population, adults, children).

[9] i.e. a high residue corresponding to the true MRL but relating to the residue definition for dietary risk assessment, see Chapter 2.3

Case 2b $IESTI = LP_{bw} \times MRL \times v \times CF \times PF$

Because of the substantial uncertainty in the values of the unit weight and the error that using the unit weight creates in the case 2a equation (see Chapter 2.5) , , it could be considered to remove the unit weight from the IESTI equations.

Option 3: as option 2, but unit weight removed:

Case 1 = case 3 $IESTI = LP_{bw} \times MRL \times CF \times PF$

Case 2a=case 2b $IESTI = LP_{bw} \times MRL \times v \times CF \times PF$

Please note that in Chapter 3.1 a preliminary analysis is presented on the number of MRLs that would be acceptable when using the equations in option 1 and 2, or 3 instead of the current equations.

Questions to be answered:

- Q14: Would you prefer option 1, 2 or 3 over the current IESTI equations?
- Q15: Are there other options that could be considered?

2.7 How to deal with situations where residues are <LOQ?

Sometimes residue field trials at cGAP show residues in the raw agricultural commodity below the LOQ for all samples. This may represent a zero-residue situation or a situation where residues are present but below the LOQ. The zero-residue situation is the situation where no residues are expected even if higher doses or shorter PHIs are applied. If other crop field trials at higher doses or shorter PHI show residues above LOQ or metabolism studies indicate the possibility of residues at higher doses the zero-residue situation is not confirmed. This could be caused by the type of application (e.g. herbicide treatment below trees, seed treatment) or the timing of application (early in the growth season before the harvestable part of the crop has formed) or because degradation is very rapid and no relevant residues are found at any time.

How to deal with this situation?

a) For the situation where residues are found below LOQ, but the zero-residue situation is not confirmed at higher doses or lower PHI or in metabolism studies (situation a), the MRL is set at the LOQ and the dietary risk assessment is performed with STMR and HR = LOQ[10]. In this case it seems appropriate to replace the HR and STMR by the MRL.

[10] If residues can be confirmed to be at levels equal to or less than the limit of detection, US-EPA would generally use that as the benchmark, not the LOQ.

Whether a variability factor, a conversion factor and/or processing factor is appropriate here needs to be discussed.

b) For the situation where residues are found below LOQ and the zero-residue situation is confirmed at higher doses or lower PHI or in metabolism studies (situation b), the MRL is also set at the LOQ, but the dietary risk assessment is performed with STMR and HR = 0. In this case it does not seem appropriate to replace HR and STMR by MRL: working with the LOQ instead of 0 mg/kg leads to an overestimation of the exposure.

At present, it is very often unclear whether an MRL at the LOQ relates to a zero-residue situation. Therefore, as a default approach, it is proposed to use the LOQ in the IESTI equation in case the MRL is set at the LOQ for both situations.

Questions to be answered:

- Q16: Should the LOQ be used in the IESTI equation in case the MRL is set at the LOQ for both situations (STMR=HR=MRL= LOQ and STMR=HR=0 & MRL=LOQ)
- Q17: Is a variability factor, conversion factor and/or processing factor appropriate in case the residues of all composite samples lie at or below the LOQ?

2.8 How to deal with animal commodities?

Residues in feed may lead to detectable residues in animal tissues, milk and eggs, necessitating MRLs for those commodities. The residues that may arise in animal commodities are estimated based on the combined information from dietary burden calculations and livestock feeding studies.

The estimation of the STMR (or median residue) in animal commodities is based on the interpolation of the mean livestock dietary burden in a feeding study. The mean livestock dietary burden is calculated based on the median residues in all feed items. The residue in tissues, milk and eggs corresponding to the mean livestock dietary burden is interpolated either manually from the 2 closest dose levels in the feeding study (including zero dose) or statistically based on linear regression using all dose levels in the feeding study. The average residue level per dose level is taken from the feeding studies to estimate the STMR in muscle, fat, liver, kidney, milk and eggs.

The estimation of the HR (or highest residue) in animal commodities is based on the interpolation of the maximum livestock dietary burden . in a feeding study. The maximum livestock dietary burden is calculated based on the highest residues in individual feed items, although median residues in feed items are used in case of bulking/blending (e.g. pre-harvest treated seeds, grains) and or processed commodities (e.g. fruit pomace). The residue in tissues, milk and eggs corresponding to the maximum livestock dietary burden is interpolated either manually from the 2 closest dose levels in the feeding study (including zero dose) or statistically based on linear regression using all dose levels in the feeding study. The highest residue level per dose level is taken from the feeding studies to estimate the HR in muscle, fat, liver, kidney, and eggs.

A livestock feeding study on lactating cows and/or laying hens normally comprises 4 different dose levels: 0 , 1 , 3 and 10 . Feeding studies with lactating cows consist of 1 untreated (control) animal per study and 3 anim als per dose group. Feeding studies with laying hens consist of 1 untreated (control) animal per dose level (3 to 4 per study) and 3 groups of 3 hens per dose level. Milk and eggs are collected twice daily during the dosing period (28 days). PM and AM milk is pooled per day and per cow and eggs are pooled per day and per group of 3 hens. Milk and tissues of the individual cows are analysed separately, while the eggs and tissues of the hens are pooled per group of 3 hens. For cow and hen tissues 3 analysis r esults are available per dose level. For milk and eggs, 3 analysis results are available per day per dose level.

The estimation of the MRL in animal commodities is based on the interpolation of the maximum livestock dietary burden in a feeding study. In case the residue definition for animal commodities for enforcement and dietary risk assessment is the same, the MRL can be derived from the highest residue for tissues and eggs and the mean residue for milk (both based on the maximum livestock dietary burden) . However, if the residue definition is different, a separate calculation needs to be conducted for MRL setting and a highest residue for tissues and eggs and the mean residue for milk (both based on the maximum livestock dietary burden) needs to be derived, which is based on the residue for enforcement.

The OECD MRL calculator is not used in estimating the MRL in animal commodities , since residues obtained in a feeding study generally are not used direc tly but are used to interpolate the residue at the maximum livestock dietary burden . The Codex MRL for animal commodities is based on rounding up of the highest residue to the nearest figure (e.g. 0.63 becomes 0.7). This policy is the same as used in the O ECD MRL calculator: 0.01-0.015-0.02-0.03-0.04-0.05-0.06-0.07-0.08-0.09-0.1 etc. MRLs for milk are based on whole milk, even if the pestic ide in question is fat soluble and MRLs for milk are derived by rounding up the STMR to the nearest figure.

The Codex MRL for meat is based on muscle residues in case of non -fat soluble pesticides and based on fat residues in case of fat soluble pesticides. At EU level the MRL setting policy for meat has been changed recently: MRLs will be set for muscle and for fat. For meat, which is a mixture of muscle and fat, the MRL has to be calculated, considering the fat content of the mixture and the MRLs for the individual components (fat and muscle). Both Codex (JMPR) and EU use the HR (fat) and HR (muscle) to estimate dietary exposure from meat by assuming 80% of the meat consumption is actually meat muscle consumption and 20% of the meat consumption is meat fat consumption (90% muscle, 10% fat in case of poultry meat).

Currently, the IESTI for milk is estimated using case 3 e quations (STMR), while the IESTI for all other animal commodities is estimated using case 1 equations (HR). The STMR and HR are based on the residue definition for dietary risk assessment (for animal commodities). In both equations the variability factor i s not used (or v = 1). If the IESTI is changed, it means, the STMR and HR are replaced by the MRL and no variability factor is used.

For dietary risk assessment, the residue in meat (mixture of muscle and fat) is needed. If the MRL is set for muscle and f at separately these values can be used in the IESTI equations by assuming a 80/20 muscle/fat ratio (mammalia n meat) and a 90/10 muscle/fat ratio (poultry meat). However, if the MRL is set for meat (based on muscle residues only in case of non -fat soluble pesticides and based on fat residues only in case of fat soluble pesticides) an IESTI calculation based on the MRL would not be easily envisaged.

Questions to be answered:

- Q18: How could an IESTI calculation based on the MRL be performed if the MRL is set for meat?

3 How does changing the IESTI equations affect the level of protection that is provided by MRL-setting?

It is important to understand how intakes estimated using the IESTI equations relate to real intakes , in order to decide whether consumer safety is sufficiently taken into account in the process of MRL-setting. As stated in the Introduction, the IESTI equations aim at ensuring there is an appropriate level of protection and in doing so targets a particular subset of the population, namely those persons that are actually eating the commodity for which the MRL is requested.

In 2007, responding to a request by the European Commission, the EFSA PPR Panel published an opinion [EFSA, 2007] in particular on:

- The conservatism of the IESTI equation [FAO, 2002] with respect to the percentage of the total European population protected;
- The sensitivity – in terms of probability of exceeding the ARfD – to variation and uncertainty in each of the parameters of the IESTI model.
- The effect of replacing the HR with other estimates of the highest residues e.g. the MRL on the outcome of the equation.

In accordance with the terms of the Commission request, the PPR Panel [EFSA, 2007] defined the 'level of protection (LoP)' as the percentage of person-days with intakes at or below the Acute Reference Dose. An LoP of 100% would therefore be the ideal outcome.

To address the question of how conservative the IESTI equation is with respect to people who consume one commodity at the level of the MRL [11] and other commodities at monitoring levels, the PPR panel estimated acute dietary intakes both by probabilistic modelling and by calculating IESTI's [EFSA 2007] . The final assessment was performed by 'bench-marking' the outcome of each IESTI calculation to the probabilistic distribution. The PPR panel conducted assessments for 92 scenarios representing 11 pesticides, 2 countries and mainly young children.

Not unexpectedly, in all cases the specific LoP for each scenario varies widely between different countries and pesticides, and also between commodities.

The PPR panel's assessments showed that 81 scenarios would qualify for MRLs with the current IESTI equations (STMR or HR and EU variability factors of 5 and 7 for case 2a and 2b). For some of these scenarios, the estimated LoP was between 90 and 99% but most scenarios were above 99% and many above 99.9%. The estimates are very uncertain but probably conservative, i.e. probably underestimate the true LoPs.

On average, the commodity at the MRL contributed over 90% of the intake in these scenarios.

Although the analysis by the PPR Panel concerned only 11 pesticides and 2 countries, the results make it plausible that the IESTI calculation results in MRLs that provide in general a LoP >99%. Based on this analysis, it is proposed to consider the proportion of

[11] Adjusted to the dietary intake residue definition

the number of MRLs for which the calculated old and new IESTI exceeds the ARfD as a reasonable measure for the change in the LoP caused by using the new IESTI equations.

Changing the variability factor from 5 and 7 (EU procedure) to 3 (JMPR procedure) increased the number of pesticide/country/commodities qualifying for MRLs from 81 to 86. Because the proportion of scenarios added was small, it did not markedly change the overall distribution of LoPs in the assessments. The changes occurred at the lower end of the distribution: 4 of the 5 added scenarios had relatively low LoPs at or below 99%.

Changing the current IESTI equation (EU procedure) by replacing the HR with the MRL[11] decreased the number of pesticide/country/commodities qualifying for MRLs from 81 to 73. This had a slightly larger effect on the overall dis tribution of LoPs than changing the variability factor. The changes occurred at the lower end of the distribution: 7 of the 8 deleted commodities had estimated here again relatively low LoPs around 99%[12].

The LoP is also for an important part driven by th e magnitude of the exposure (as estimated by the IESTI equation) relative to the ARfD. For this reason the PPR Panel also explored the relationship between the LoP and the IESTI/ARfD ratio. A clear relationship was shown and the LoP tended to be around 99% when the IESTI/ARfD ratio is close to 1 (= when the IESTI outcome is –almost- identical to the ARfD) . When the IESTI outcome is < ARfD the LoP goes up to >99.99%. The Panel judged, after evaluating the uncertainties in the assessment, that its quantitativ e results are most likely to be conservative, i.e. overestimating intakes and underestimating the LoP.

It can therefore be concluded for the scenarios investigated [13] that the IESTI is largely doing what it is supposed to do, namely assuring that food contai ning residue at the level of the MRL is safe. **It is however clear that the LoP is specific for a particular MRL and varies widely between different countries and pesticides, and also between commodities.**

The view of the European Commission is that any change to the current equations should result in an **over-all** LoP that is identical, or higher than the current LoP.

Although it is noted that changing from HR to MRL and changing the variability factors at the same time may lead to the loss of some MRLs and to acceptance of other MRLs at the same time, it is proposed to take the **number of MRLs** that would pass the dietary risk assessment in the new versus the old methodology as a reasonable measure for the change in LoP. Such an assessment should be performed using MRLs that have been derived by the OECD calculator. This is addressed in a limited impact analysis in paragraph 3.1.

If we take the proportion of the number of MRLs as reasonable measure for the change in LoP, it may be unnecessary to again benchmark IESTI outcomes to real in take distributions.

[12] It is noted that nowadays MRLs are calc ulated using the OECD MRL calculator and therefore nowadays MRLs are generally higher than in 2007. The number of acceptable MRLs will most probably decrease when compared to the number derived in the 2007 PPR Panel Opinion.
[13] 92 scenarios representing 11 pesticides, 2 countries and mainly young children

- Q19: Is the number of MRLs that would pass the dietary risk assessment in the new versus the old methodology providing some confidence that the LoP has not changed drastically, in other words is this number a reasonable measure for the change in LoP??
- Q20: Do you have other suggestions for estimating the change in LoP?

3.1 Impact on MRLs

Any change of the IESTI equation may have impact on the number of MRLs that pass a dietary risk assessment.

Impact assessments were conducted using the model developed by EFSA (PRIMo – Pesticide Residue Intake Model, EU-PRIMo rev 2) and the JMPR 2014 IESTI model. In this assessment the number of acceptable MRLs, obtained with the current IESTI equation, were compared to those obtained with the new IESTI equations (option 1, 2 and 3 equations in paragraph 2.6).

Note: The large portions in the PRIMO rev 2 and the JMPR IESTI model are given as kg/person, although in some cases these large portions were derived from a distribution as kg/kg bw bw. Therefore no distinction can be made between option 1 & 2 equations (paragraph 2.6) and the impact on MRLs is made using the currently available large portions.

In 2014, ANSES (French Agency for Food, Environmental and Occupational Health & Safety) performed a preliminary impact assessment on substances evaluated by the EU with the PRIMO rev 2 model for option 1 & 2 equations (HR & STMR replaced by MRL, variability factor 1 for case 1&3, variability factor = 3 for case 2a&2b, LP as in the model, may be based on kg/person or kg/kg bw distributions) . In case the residue definition for enforcement was different from the residue definition for dietary risk assessment, the MRL was multiplied by a conversion factor to predict the residue for dietary risk assessment.

The preliminary study by ANSES focused on 20 active substances: 1-MCP, Captan, Dimethenamid-P, Dimoxystrobin, Flonicamid, Flusilazole, Flutriafol, Folpet, Lambda-cyhalothrin, Metalaxyl, Metaldehyde, Metazachlor, Methoxyfenozide, Pethoxamid, Picolinafen, Pirimicarb, Propamocarb, Prothioconazole, Thiacloprid, Tribenuron. This selection was based on a final Reasoned Opinion (RO) published by EFSA in 2014 [14]. For these 20 active substances 965 MRLs were proposed of which 409 MRLs were at the LOQ (STMR or HR = MRL, 291 of vegetable origin, 118 of animal origin) and 556 MRLs were higher than the LOQ.

For 14 MRLs (1.5% of assessed cases) a different conclusion would be drawn when using the current or the option 1 & 2 IESTI equation: for 9 MRLs no authorisation would be granted using the current IESTI equations, but an authorisation would be granted using the new IESTI equations. For 5 MRLs an authorisation would be granted using the

[14] On October 2014, for 165 approved active substances a final Reasoned Opinion (RO) has been published by EFSA and for 51 of these active substances an ARfD has been proposed. Among these 51 active substances, MRLs have been proposed on the basis of OECD calculator for 20 active substances.

current IESTI equation, but no authorisation would be granted using the option 1&2 IESTI equations.

Using the **current EFSA IESTI equations** (STMR or HR, case 1, 2a, 2b, 3, variability factor 1, 5 or 7), 931 of the 965 proposed MRLs are considered acceptable because they do not exceed the ARfD. The new IESTI equations may result in a higher or lower exposure because STMR or HR is increased to the MRL for all three options, while variability factor stays the same or is decreased from 5 or 7 to 3.

Using the **option 1 & 2 IESTI equations** (MRL, case 1=3, 2a, 2b, variability factor 1 or 3), 930 of the 965 proposed MRLs are acceptable (1 MRL lost). However the acceptable MRLs for the new IESTI equation are not in all cases the same MRLs as those considered acceptable by the current IESTI equation.

A total of 17 of the 965 proposed MRL (1. 7% of assessed cases) result s in a different conclusion when using the current or the option 1 & 2 IESTI equations. Among these 17 "differing" pairs, 8 concern an ARfD exceedance with the current IESTI equation , which is no longer detected when using the option 1 & 2 IESTI equation s (0.82% of the assessed cases), and 9 concern an ARfD exceedance detected when using the option 1 & 2 IESTI equation, which is not detected when using the current IESTI equations (0.93% of the assessed cases).

- The 8 MRLs considered acceptable with the new equations but not with the current are: pirimicarb/leek, propamocarb/lettuce , lambda-cyhalothrin/apples, lambda-cyhalothrin/pears, pirimicarb/apples, pirimicarb/pears, propamocarb/ leek and thiacloprid/kale.
- The 9 MRLs considered acceptable with the current equations but not with the new are: flusilazole/bovine meat, pirimicarb/lam b's lettuce, pirimicarb/rocket - rucola, lambda-cyhalothrin/spinach, thiacloprid/blackberries, thiacloprid/raspberries, folpet/table grapes, lambda -cyhalothrin/aubergine, and propamocarb/scarole.

In 2015 RIVM performed a preliminary impact assessment on sub stances evaluated by the JMPR with the 2014 JMPR IESTI model for option 1&2 or option 3 IESTI equations. The preliminary study by RIVM focused on substances evaluated by the 2011, 2012, 2013 and 2014 JMPR, because MRLs from this period were derived by usin g the OECD MRL calculator. In this period a total of 89 substances were evaluated and ARfDs were considered necessary for 62 of these active substances. For 15 of these 62 active substances the residue definition for enforcement was different from the resi due definition for dietary risk assessment. RIVM only focussed on the remaining 47 active substances for which the residue definition for enforcement was equal to the residue definition for dietary risk assessment: Benzovindiflupyr, buprofezin, carbofuran, chlorpyrifos-methyl, Clothianidin, cycloxydim, beta -cyfluthrin, cypermethrins, cyproconazole, cyromazine, Dichlobenil, dichlorvos, dicofol, difenoconazole, Dimethomorph, diquat, dithianon, emamectin benzoate, etofenprox, fenbuconazole, Fenpropathrin, fenp yroximate, fenvalerate, Fluensulfone, fluopyram, flutriafol, fluxapyroxad, imidacloprid, indoxacarb, malathion, metamidophos, Methoxyfenozide, Phorate, Phosmet, profenofos, Propamocarb, Prothioconazole, pyraclostrobin, Sedaxane, sulfoxaflor, tebuconazole, Thiamethoxam, tolfenpyrad, Triadimenol, triazophos, triflumizole, Triforine. RIVM only focussed on the MRLs derived for plant commodities. For these 47 active substances 377 MRLs were proposed for plant commodities of which

44 MRLs were at the LOQ (STMR or HR = MRL) and 333 MRLs were higher than the LOQ. RIVM focussed only on the 50 MRLs where the ex posure was higher than 20% ARfD. For the remaining 327 MRLs below this exposure (44 MRLs at the LOQ and 283 MRLs > LOQ) it was assumed that the conclusion on ac ceptability of the MRL would be the same when using the current IESTI equation or the option1&2 or option 3 IESTI equations.

Using the **current JMPR IESTI equations** (STMR or HR, case 1, 2a, 2b, 3, variability factor 1 or 3), 368 of the 377 proposed MRLs are considered acceptable because they do not exceed the ARfD. The new IESTI equations will always result in higher exposure because STMR or HR is increased to the MRL for all three options, while variability factor stays the same.

Using the **option 1&2 IESTI equations** (MRL, case 1=3, 2a, 2b, variability factor 1 or 3), 348 of the 368 acceptable MRLs remain acceptable (20 MRLs lost; 5.4% of cases). These 20 MRLs concern: chlorpyrifos -methyl/wheat, dichlorvos/wheat, dimethomorph/spinach; dithianon/grapes; dithianon/plums; emamectin benzoate/head lettuce; emamectin benzoate/leaf lettuce; fenpropathrin/strawberries; fenpropathrin/plums; fenpropathrin/sweet peppers; fenpyroximate/plums; fenpyroximate/cherries; fluopyram/leaf lettuce; flutriafol/grapes; indoxacarb /leaf lettuce; prothioconazole/currants; pyraclostrobin/currants; sulfoxaflor/leaf lettuce; tebuconazole/grapes; tolfenpyrad/tea.

Using the **option 3 IESTI equations** (MRL, case 1 =3 or case 2a =2b, no unit weight, variability factor 1 or 3), 346 of the 368 ac ceptable MRLs remain acceptable (22 MRLs lost; 6.0% of cases). These 22 MRLs concern the same MRLs as for option 1&2 IESTI equations and in addition: dithianon/apples and pyraclostrobin/plums.

These calculations show that 5.4%-6.0% of the Codex MRLs will no longer be acceptable when using option 1&2 or option 3 equations. Detailed results are given in appendix 5.

Since only the cases were evaluated, where the exposure was > 20% ARfD, more MRLs might be lost with option 1&2 and option 3 equations for case 3 bulked/blended commodities (tea, cereals), because the increase for exposure for option 1&2 and option 3 equations for case 3 bulked/blended commodit ies is often higher than a factor 5. So the wrong cut-off point was chosen. It might be useful to repeat these calculations for exposures between 10% -20% ARfD or for all case 1 and case 3 commodities in the selection to get the full impact assessment.

Based on these impact assessments, option 1&2 equations and option 3 equations result in the same number of MRL losses for JMPR, while for EU only a limited effect on the number of MRLs is seen with option 1&2 equations (option3 equations not verified). Option 3 equations seems to be the best choice, because of the independence of the unit weight and the possibility to use the large portion on a kg/kg bw basis in the equations without introducing errors as in option 2 equations.

Replacing STMR by MRL in the case 3 commodities (cereals, tea, fruit juices) has quite an impact on the number of MRLs for these commodities. The current dietary risk assessment assumes bulking and blending of these commodities before it goes to trade and therefore uses the median as best estimate for the exposure. If the median is indeed the best estimate for the residue in bulked and blended commodities, and if it is agreed that a residue directly related to the MRL should be used in the dietary risk assessment, this raises the question whether also for these commodities the MRL should be based on a high estimate based on field trial data at cGAP by using the OECD calculator, or on another estimate.

Risk managers may want a pilot period to assess the impact of the IESTI change by running the old and new equation for a period of e.g. 1 year next to each other. In addition, a pilot period to set up databases and other communication tools to communicate the input parameters for the IESTI equation to interested parties would be needed. After this pilot period an expert meeting could discuss the outcome of the pilot and establish the appropriate IESTI equations and the appropriate communication tools.

Questions to be answered:

- Q21: Replacing STMR by MRL in the case 3 commodities (cereals, tea, fruit juices) has quite an impact on the number of MRLs for these commodities. Would it be appropriate to reconsider the MRL setting process for these commodities?
- Q22: Should additional data be checked during the pilot period?
- Q23: Should specific additional data be generated during the pilot period?

4 What is the appropriate IESTI equation(s) for food safety inspection services?

Although the IESTI equation was originally meant for dietary risk assessment for the purpose of authorisation of use and MRL setting of pesticides, the IESTI is also used by food safety inspection services for risk assessment when a batch is found to contain a residue level that exceeds the MRL. In this case, the batch will be destroyed when consumption may lead to exposure above the ARfD. In some cases other parties (e.g. retail, NGO) find that the exposure based on residues found by the inspection services, calculated with IESTI, exceeds the ARfD even though the MRL is not exceeded. In such situations, food safety inspection services cannot act, because the legal limit is not exceeded. Replacement of the HR in the IESTI equations by the MRL (adjusted) at the time of authorisation would solve this problem.

It needs to be discussed whether the IESTI should be used at all by food safety inspection services. When applying the IESTI for prospective risk assessment, one is in principle considering the risk to a large number of people since the Large Portions in the IESTI equation are deduced from the 97.5th percentile consumption for the population group of interest which is randomly distributed over the whole country. When looking at safety for a single batch, the number of consumers involved may be quite small, making it difficult to interpret the meaning of an exceeding of the ARfD for a surveillance sample lot as calculated by IESTI.

However, if the use of the IESTI equations by food safety inspection services is desired, a number of issues around the input parameters need to be further discussed, as presented below.

Since food safety inspection services do not want to throw away food that could be safely consumed despite an MRL exceedance, it could be discussed whether food safety inspection services could use a lower large portion from their national food survey instead of the higher globally harmonised large portion (see Chapter 2.4).

When the IESTI equations are used by food safety inspection services, the MRL should be replaced by the residue as measured and reported for a sampled lot.

When enforcing the MRL, sampling protocols are defined within legislation or by Codex to perform analysis on composite samples (homogenised samples of at least 1-2 kg or at least 12-24 units) and not on individual units. It should be further discussed if food safety inspection services can use the same variability factors, since their samples come from mixed lots (not all units in the composite sample come from one field or treated units may be mixed with non-treated units) and therefore the unit-to-unit variability was shown to be higher [EFSA, 2007].

However, it seems appropriate that for risk assessment, food safety inspection services use the same conversion factors and the same processing factors as were used for authorisation of use and MRL setting. In case an overall multiplication factor (MF) is preferred for authorisation and MRL setting, it should be discussed whether food safety inspection services can use the same multiplication factor.

In the PRIMo model, a 'Threshold MRL' or Critical Commodity Pesticide Concentration (CCPC) is calculated. This is the maximum concentration of a given pesticide residue that can be present in a commodity without exceeding the ARfD, and this is used by food safety inspection services to quickly assess whether a lot exceeding the MRL is a concern for public health.

Questions to be answered:

- Q24: Is it acceptable that food safety inspection services use the IESTI equations and / or 'Threshold MRL' or 'Critical Commodity Pesticide Concentrations' for assessment of the safety of a single lot, using the concentration of the residue measured in the sample?
- Q25: Is it acceptable that food safety inspection services use the same variability, conversion and processing factors as used for authorisation of use and MRL setting?
- Q26 Would it be acceptable for food safety inspection services to use a lower large portion from their national food survey instead of the higher globally harmonised large portion (see Chapter 2.4)?

4.1 How to make the input parameters available to food safety inspection services and other parties?

In order to remove trade barriers it is important to make the input parameters needed for the application of the IESTI equation available to food safety inspection services and other parties. These parameters include large portions, unit weights, variability factors, processing factors, conversion factors, 'Threshold MRLs' and, in case the use of a multiplication factor combining variability, processing and conversion factors is supported, where necessary, also the mean and corresponding standard deviations of these factors on the ln scale.

Questions to be answered:

- Q27: Can we agree that lists of harmonised input parameters (large portions, variability factors, processing factors, conversion factors, 'Threshold MRLs') should be established and be made available for both authorisation and enforcement purposes?
- Q28: Could Codex (FAO/WHO) be the body responsible for gathering the input parameters?
- Q29: What would be an appropriate time schedule to update or re-evaluate such a database?
- Q30: What would be the procedure if different residue definitions, processing factors and/or conversion factors are derived between Codex and other regulatory bodies in the world, e.g. due to different policies or due to different use patterns?

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Appendix 1: How to convert the residue for enforcement into the residue for dietary risk assessment?

General procedure

For a number of pesticides, the residue definition for dietary risk assessment is not the same as the residue definition for enforcement, but includes some additional metabolites:

Residue (dietary risk assessment) = Residue (enforcement) + metabolite A + metabolite B.

Example: spinetoram. The residue definition for enforcement is spinetoram (sum of XDE-175-J and XDE -175-L), while the residue definition for dietary risk assessment is the sum of spinetoram (sum of XDE -175-J and XDE-175-L) and the N -demethyl-175-J (ND-J) and N-formyl-175-J (NF-J) metabolites, expressed as spinetoram.

Supervised field trials on grapes are available where all residues have been measured.

RAC: Residue for enforcement: 10 <0.02, 0.021, 0.03, 0.037, 0.043, 0.045, 0.075, 0.114, 0.12, 0.27, 0.33 mg/kg (n=20)

MRL OECD calculator = 0.411 mg/kg, rounded 0.5 mg/kg.

Corresponding measured residues for dietary risk assessment in the RAC:

11 <0.04, 0.051, 0.057, 0.063, 0.065, 0.095, 0.134, 0.153, 0.36, 0.418 mg/kg (n=20)

The HR = 0.418 mg/kg would be used in the current IESTI equation.

If it is considered appropriate to utilise residues at the level of MRL in estimating short-term exposure with an IESTI, the residue levels need to be adjusted to the corresponding levels for dietary intake calculation, i.e. the MRL may be based on levels of parent compound only while for dietary intake calculation the residue may be defined as parent plus some metabolites.

The first option could be to use the residue dataset according to dietary risk assessment as input for the OECD MRL calculator to provide a 'surrogate-MRL', i.e. a high residue corresponding to the true MRL but relating to the residue definition for dietary risk assessment.

In the spinetoram example (11 <0.04, 0.051, 0.057, 0.063, 0.065, 0.095, 0.134, 0.153, 0.36, 0.418 mg/kg) this would lead to a 'surrogate-MRL'of 0.52 mg/kg, rounded 0.6 mg/kg (OECD calculator).

However, when this option is applied , it will not be possible for food safety inspection services to correct the analytical results from individual enforcement or monitoring samples to the residue definition for dietary risk assessment.

To also accommodate the needs for food safety inspection se rvices a second option could be to use a conversion factor to convert the residue for enforcement into the residue for dietary risk assessment. Currently this procedure is used within EU and the median conversion factor is taken.

For the spinetoram example:

RAC: Residue for enforcement: 10 <0.02, 0.021, 0.03, 0.037, 0.043, 0.045, 0.075, 0.114, 0.12, 0.27, 0.33 mg/kg (n=20)

RAC: Residue for dietary risk assessment: 11 <0.04, 0.051, 0.057, 0.063, 0.065, 0.095, 0.134, 0.153, 0.36, 0.418 mg/kg (n=20)

For those samples were a residue could be measured above the LOQ, t his would lead to residue definition conversion factors (CF_{RD}) of 1.70, 1.54, 1.47, 1.44, 1.27, 1.18, 1.28, 1.33, 1.27 with median CF_{RD_RAC} = 1.33 based on residue for dietary risk assessment divided by residue for enforcement for individual samples. In this case MRL CF_{RD} would lead to 0.5 1.33 = 0.66 mg/kg.

The conversion factor should be made available to food safety inspection services , so they can repeat the calculations on analytical re sults from individual samples. food safety inspection services would then replace the MRL CF_{RD} v with R CF_{RD} v, where R = is the residue measured in the sample exceeding the MRL and reported by food safety inspection services.

Special cases

In some cases special dietary risk assessments are needed where it is not possible to perform an IESTI calculation based on the MRL corrected by a conversion factor.

- Some pesticides have more than one residue definition for dietary risk assessment, e.g. one for the parent compound and one for the metabolite, to be set against their respective ARfDs. Examples SDS-3701 (chlorothalonil), triazole derived metabolites (bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, propiconazole, myclobutanil, tebuconazole, triadimefon, triadimenol), 3,5,6-trichloropyridinol (chlorpyrifos), melamine (cyromazine), ETU (dithiocarbamates) and PTU (propineb).
- Other pesticides have special residue definitions for dietary risk assessment, where the difference in toxicity between parent and metabolites is taken into account. Examples dimethoate/omethoate and glufosinate-ammonium/NAG/MPP.

It is outside the scope of this workshop to discuss these special cases. The examples show that a residue conversion factor is not appropriate in all cases.

Appendix 2: How to deal with processed commodities?

Predicting residues in processed commodities from residue in the RAC for the case where the residue definition for enforcement is equal to the residue definition for dietary risk assessment

For the purpose of authorisation of use and MRL setting, dietary risk assessment for processed commodities is generally conducted by prediction/estimation of the residue in the processed commodity through multiplication of the residues in the RAC by the peeling or processing factor for that particular processed commodity (PF). The peeling or processing factor accounts for residue changes by peeling or processing. The mathematical formula for PF = residue in a specified peeled or processed commodity / residue in the RAC. Processing factors are derived from specifically conducted processing studies, where industrial and household processing procedures are conducted at laboratory scale.

Residues in the raw edible portion (REP, i.e. flesh or pulp) are generally much lower than in the raw agricultural commodity for those raw agricultural commodities where the peel is removed before consumption and where the pesticides are known to stay predominantly on the surface. Commodities where this is the case are citrus fruits, bananas, avocado's, mango's, papaya's and melons.

In the present situation, JMPR generally does not define a processing factor for raw edible portion but uses the residues as measured in the raw edible portions to estimate STMR and HR. However, when this option is applied, it will not be possible for food safety inspection services to correct the analytical results from individual enforcement or monitoring samples (RAC) to the residue in the processed commodity.

A second option would be to use a processing factor for peeling. Processing factors for peeling are currently used within EU and the median processing factor is taken when more processing studies are available for one commodity/pesticide combination.

In case the STMR or STMR-P and HR or HR-P needs to be replaced by the MRL, the MRL could be multiplied by the peeling or processing factor to account for residue changes by peeling or processing. Since the residue definition for enforcement is equal to the residue definition for dietary risk assessment, the residue definition conversion factor does not appear in this equation (CF_{RD} = 1). This is depicted schematically below

	Residue definition **Enforcement (RD ENF) = risk assessment (RD RA)**
Raw agricultural commodity (RAC)	PF_PP PF_REP **MRL**
Raw edible portion (REP)	input for $IESTI_{new}$ (unprocessed products) MRL x PF_REP
Processed product (PP)	**MRL processed product** input value for $IESTI_{new}$ (processed product) MRL x PF_PP

Example: Pesticide YY in/on bananas. The residue definition for enforcement is the same as the residue definition for dietary risk assessment, namely parent.

Supervised field trials on bananas are available for the RAC (raw agricultural commodity) and the REP (raw edible portion).

RAC: Whole fruit: 0.066; 0.099; 0.103; 0.220 mg/kg (n=4) (indoor trials)

REP: Pulp: 0.043; 0.038; 0.050; 0.122 mg/kg (sorted as for whole fruit)

MRL OECD = 0.39 mg/kg, rounded 0.4 mg/kg; proposed MRL for whole bananas is 0.4 mg/kg.

Currently JMPR uses the actual data in the raw edible portion for the selected trials to carry out the acute dietary risk assessments. The HR_{pulp} = 0.122 mg/kg would currently be used in the IESTI equation. Another option is, to derive a processing factor for peeling. One could use the same trials to derive a processing factor for peeling (n=4). But since there were more trials available (conducted according to GAP) to derive such a processing factor, a more robust processing factor could be derived by taking other trials into account.

Eight trials (4 indoor and 4 outdoor trials) were available where processing factors for peeling could be derived: 0.37, 0.38, 0.40, 0.48, 0.49, 0.50, 0.55, 0.65, based on residue in the raw edible portion divided by residue in the raw agricultural commodity. The median processing factor (PF_{REP}) for peeling derived from these trials is 0.49. In this situation the residue used in the IESTI equation would be MRL PF_{REP} = 0.4 0.49 = 0.20 mg/kg. This value is lower than the MRL itself.

Predicting residues in processed commodities from residue in the RAC for the case where the residue definition for enforcement is different to the residue definition for dietary risk assessment

In case the residue definition for enforcement is different from the residue definition for dietary risk assessment two types of processing factors can be derived: a processing factor based on the residue for enforcem ent (PF_{ENF}) or a processing factor based on the residue for dietary risk assessment (PF_{RISK}).

As equation:

where

PF_{RISK} = processing factor based on the residue definition for dietary risk assessment
$(C+M)_{REP}$ = sum of parent (C) plus metabolites (M), expressed as parent, as measured in the raw edible portion (i.e. peeled orange)
$(C+M)_{RAC}$ = sum of parent (C) plus metabolites (M), expressed as parent, as measured in the raw agricultural commodity (i.e. whole fruit orange)
PF_{ENF} = processing factor based on the residue definition for enforcement
C_{REP} = parent as measured in the raw edible portion (i.e. peeled orange)
C_{RAC} = parent as measured in the raw agricultural commodity (i.e. whole fruit orange)

In case the STMR or STMR -P and HR or HR -P needs to be replaced by the MRL, the MRL could be replaced by a 'surrogate-MRL' as explained in appendix 1 and then be multiplied by a peeling or processing factor based on the residue definition for dietary risk assessment for that particular peeled or processed commodity : 'surrogate -MRL' PF_{RISK_PP} (option 1).

Another possibility is to multiply the MRL by a residue definition conversion factor (CF_{RD}) and a peeling or processing factor (PF) . The residue definition conversion factor (CF_{RD}) converts the residue for enforcement into the residue for dietary risk assessment (see appendix 1). Conversion factors can be derived for the RAC, the raw edible portion (or specified processed commodities (CF_{RD_RAC}, CF_{RD_REP}, CF_{RD_PP}). Because of the different types of conversion factors and processing factors, there are two additional options to correct the MRL.

- The second option is to multiply the MRL by the processing factor for enforcement (PF_{ENF_PP}) and then by the conversion factor for that particular processed commodity (CF_{RD_PP}): MRL PF_{ENF_PP} CF_{RD_PP}.
- The third option is to multiply the MRL by the conversion factor for the RAC (CF_{RD_RAC}) and then multiply by the processing factor for dietary risk asses sment for that particular processed commodity (PF_{RISK_PP}): MRL CF_{RD_RAC} PF_{RISK_PP}.

Both options are depicted in the schemes below:

Option 2: First multiply MRL by processing factor and then by conversion factor

	Residue definition	
	Enforcement (ENF)	**Dietary risk assessment (RISK)**
Raw agricultural commodity (RAC)	PF_ENF_PP ↓ PF_ENF_REP ↓ **MRL** → CF_RD_RAC	input for $IESTI_{new}$ (unprocessed products) MRL x PF_ENF_RAC x CF_RD_RAC
Raw edible portion (REP)	→ CF_RD_REP	input for $IESTI_{new}$ (unprocessed products) MRL x PF_ENF_REP x CF_RD_REP
Processed product (PP)	**MRL processed product (MRL x PF_ENF_PP)** → CF_RD_PP	input value for $IESTI_{new}$ (processed product) MRL x PF_ENF_PP x CF_RD_PP

Option 3: First multiply MRL by conversion factor and then by processing factor

	Residue definition	
	Enforcement (RD ENF)	**Risk assessment (RD RA)**
Raw agricultural commodity (RAC)	PF_ENF_PP ↓ **MRL** → CF_RD_RAC	input for $IESTI_{new}$ (unprocessed products) MRL x CF_RD_RAC x PF_RISK_RAC PF_RISK_REP ↓ PF_RISK_PP ↓
Raw edible portion (REP)		input for $IESTI_{new}$ (unprocessed products) MRL x CF_RD_RAC x PF_RISK_REP
Processed product (PP)	**MRL processed product (MRL x PF_ENF_PP)**	input value for $IESTI_{new}$ (processed product) MRL x CF_RD_RAC x PF_RISK_PP

Example: Pesticide ZZ in oranges. The residue definition for enforcement is parent, while the residue definition for dietary risk assessment is the sum of parent and metabolite, expressed as parent.
Supervised field trials on whole fruit oranges are available where all residues have been measured.
Residue for enforcement: 0.07; 0.11 #; 0.12; 0.13 #; 0.18; 0.20 #; 0.21; 0.21; 0.24; 0.56#; 0.58 mg/kg (n=11) -
MRL OECD calculator = 0.927 mg/kg, rounded 1 mg/kg.
Corresponding residues for dietary risk assessment in the whole fruit:
0.23; 0.24; 0.29; 0.34; 0.34; 0.38; 0.42; 0.44; 0.58; 0.59; 0.62 mg/kg (n=11).
'Surrogate-MRL' OECD calculator: 1.219, rounded 1.5

Corresponding residue definition conversion factors (CF_{RD_RAC}):
3.29; 2.18; 2.42; 2.62; 1.89; 1.90; 2.00; 2.10; 2.42; 1.05; 1.07, median 2.1

Four trials were available where also the residue in the raw edible portion was measured (indicated by # in the original dataset):
Residue for enforcement: < 0.01 (4) mg/kg (n=4)
Residue for dietary risk assessment: 0.19; 0.30; 0.26; 0.04 mg/kg (n=4)
Corresponding residue definition conversion factors (CF_{RD_REP}):
>18.57; >30.00; >25.71; >4.29, median >22.1

Processing factors for peeling derived from these data.
PF_{ENF_REP} = <0.091; <0.077; <0.050; <0.018, median <0.063
PF_{RISK_REP} = 0.77; 0.88; 0.68; 0.073; median 0.73

The dietary risk assessment can then be conducted using:
Option 1: 'surrogate-MRL' PF_{RISK_REP} = 1.5 0.73 = 1.1
Option 2: MRL PF_{ENF_REP} CF_{RD_REP} = 1 < 0.063 >22.1 = 1.4
Option 3: MRL CF_{RD_RAC} PF_{RISK_REP} = 1 2.1 0.73 = 1.5

From this example it is clear that option 2 is much more sensitive to analytical limits and errors than options 1 and 3 , because the parent compound is often the compound that disappears to levels close to the limit of quantification, while the total residue (as used in option 1 and 3) still can be measured with sufficient precision.

Appendix 3: C ombined distribution of variability factor, conversion factor and processing factor into a single multiplication factor (MF)[15].

Assuming that all three factors are log normally distributed, the distribution of the product of the factors can be easily calculated. Assuming that the three constituent distributions represent true variation, and that a consumer randomly "samples" a value from each of the three distributions, the distribution of the product reflects the probability of the combined factor in that consumer.

Calculating the P95

The general formula for calculating the P95 of a distribution of a log-normally distributed factor F is:

where σ_{lnF} is the "true" standard deviation of the factor F on the ln scale.

In a limited dataset, 1.64 σ is replaced by q stdev, where stdev is the standard deviation calculated for the sample, and where q is a constant that depends on the sample size (see e.g., Aldenberg and Jaworska 2000).

Variability factor (v)

By assumption, the geometric mean of the variability factor ($GMean_v$) = 3

By assumption, the P95 of the variability factor ($P95_v$) = 5

Consequently, the dispersion factor k is 5/3=1.67

The standard deviation of v on the ln scale is calculated from [Slob, 1994]:

$$\sqrt{(\quad)} \qquad \sqrt{(\quad)}$$

This value will not change and is equal for all pesticide/commodity combinations.

Conversion factor (CF_{RD})

[15] The authors gratefully acknowledge the valuable contribution of Wout Slob (RIVM, The Netherlands) to the development of the single multiplication factor.

The conversion factor is experimentally determined from supervised field trials.

If we have a series of conversion factors, these are first ln transformed. Then the mean and standard deviation are calculated from this ln transformed dataset (using Excel functions average and stdev).

For example, we have a series of 15 conversion factors: 1. 952, 1.870, 1.714, 1.700, 1.625, 1.688, 1.541, 1.465, 1.444, 1.267, 1.382, 1.175, 1.275, 1.333, 1.267

These are ln transformed to get ln (CF_{RD}): 0.6690, 0.6257, 0.5390, 0.5306, 0.4855, 0.5232, 0.4321, 0.3819, 0.3677, 0. 2364, 0.3232, 0.1616, 0. 2430, 0. 2877, 0.2364, resulting in

$mean_{lnCF\_RD} = 0.403$
geometric mean $GMean_{CF\_RD}=e^{0.403}=1.50$
$stdev_{lnCF\_RD}= 0.155$

An estimate of the P95 of the distribution of conversion factors is:

An upper confidence bound for the P95 can be calculated by replacing the constant 1.64 by the appropriate constant q (Aldenberg and Jaworska , 2000). The estimate and upper bound of this P95 will change for every dataset (pesticide/commodity specific).

Processing factor (PF)

The processing factor is experimentally determined from processing studies.

If we have a series of processing factors, these are first ln transformed. Then the mean and standard deviation are calculated from this ln transformed dataset (using Excel functions average and stdev).

For example, we have a series of processing factors: 0.37, 0.38, 0.40, 0.48, 0.49, 0.50, 0.55, 0.56

These are ln transformed to get ln (PF): -0.9942, -0.9676, -0.9163, -0.7340, -0.7134, -0.6932, -0.5978, -0.5798,

resulting in

$mean_{lnPF} = -0.775$
geometric mean $GMean_{PF}=e^{-0.775}=0.461$
$stdev_{lnPF}= 0.163$

An estimate of the P95 of the distribution of conversion factors is:

An upper confidence bound for the P95 can be obtained by replacing the constant 1.64 by the appropriate constant q (Alderberg and Jaworska , 2000). The estimate and upper bound of this P95 will change for every dataset (pesticide/commodity specific).

The product of the P95 etimates for the three factors is: $P95_v$ $P95_{CF\_RD}$ $P95_{PF}$ = 5 1.93 0.602 = 5.81

The resulting product is not a n estimate of the P95 but is an estimate of a higher percentile (with an unknown associated percentage). This is due to the assumptions of log-normality and independence of the three sources of variability; without log - normality, the most that could be claimed is that the result of this calculation would estimate at least a P86 overall. Therefore, a better option is to multiply the distributions of the variability factor, the conversion factor and the processing factor , which results in a distribution for the combined multiplication factor (MF). This is done as follows.

First, calculate the geometric mean of the multiplication factor ($GMean_{MF}$):

$GMean_{MF}$ = $GMean_v$ $GMean_{CF\_RD}$ $GMean_{PF}$ = 3 1.50 0.461 = 2.07

Then, calculate the standard deviation of the ln transformed MF ($stdev_{lnMF}$):

√ √

Then an estimate of the 95th percentile of the distribution of MF is:

The combined P95 value (3.89) is much lower than the value (5.81) obtained by multiplying the P95 values from individual factors. The combined P95 value is however based on sample statistics (the mean and standard deviation) of limited samples and contains uncertainties. The uncertainty in the combined distribution of the MF can only readily be assessed by Monte Carlo methods (the method of replacing 1.64 by the appropriate value of q does not work here, as the combined Gmean and stdev are based on distinct samples). This needs to be elaborated further.

Abbreviations used:

$P95_{MF}$	P95 value of the multiplication factor MF (the combined distribution)
$GMean_{MF}$	Geometric mean of the multiplication factor MF (the combined distribution)
$stdev_{lnMF}$	standard deviation of the multiplication factor MF (the combined distribution) on the ln scale, based on a limited dataset
σ_{lnv}	standard deviation of the variability fact or (v) on the ln scale, based on a very large dataset

idem for variability factor (v), processing factor (PF) and conversion factor (CF_{RD}).

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Appendix 4: Large Portion

The IESTI equation includes the so called large portion (LP) which is represented by the highest 97.5th percentile of consumption for a particular commodity selected from all available national dietary surveys. [16] Different large portions are derived for relevant population groups like toddlers/young children, women of childbearing age and adults. The LP is therefore a unique value for a considered commodity which can be updated when new food consumption data become available.

At national level, the 97.5th percentiles (lp) are calculated by identifying all the days of consumption for each commodity under consideration. If the national survey is based on more than one day per subject, each day is considered independent even for the same consumer. The result is then a distribution of "n" days of consumption (or consumer*day) values and the 97.5th percentile of this distribution can be estimated. Considering N as the number of consumers in the survey, N can be lower to n if the survey is based on more than one day per subject. In such a case the national value lp is expected to protect more than 97.5% of national consumers.

At international level all national LP are collected together with the associated number of consumer*days "n". On the contrary neither the total number of subjects in the survey nor the total population in the country are considered to identify the LP value. The LP is therefore likely to protect more than 97.5% of the population for which food consumption data are available.

The reliability of high percentiles is related to the number of observations used to calculate them. Percentiles calculated on a limited number of days of consumption should be treated with caution as the results may not be statistically robust. A clear indication concerning the minimum number of observations necessary to estimate a given percentile cannot be found in the literature, because the number required depends on how much uncertainty you are prepared to tolerate. Different options can be used, none of them being a widely accepted standard. The GEMS Food Programme is collecting regularly new available national food consumption data and since 2011 the number of consumer*day n associated with the 97.5th percentile is also collected and available. In the IESTI equation the highest or most critical LP is considered. The LP should be regularly updated when new data become available. Currently no rules are established to update the LP in the IESTI equation.

Since the value and the specificity of the large portion has a significant impact on the outcome of the IESTI equation, a guidance needs to be developed how to derive the large portion. This guidance need to address the following points:

[16] Please note that the highest LP does not necessarily lead to the highest exposure (expressed as percentage of the ARfD), because the unit weights need to be taken into account. Different unit weights were reported for different countries. Therefore in the EFSA PRIMo the selection of the most critical LP is based on IESTI calculations for each survey of a country, combining the LP with the U of that country.

- the population groups for which large portions need to be derived (e.g. toddlers of 0.6-2 years, children of 2-6 yrs, adults of 20-50 yrs, elderly of >70 yrs). It would be useful to specifically define the age groups.
- the appropriate way to obtain the consumption values (e.g. single day consumption over the year with a minimum defined number of consumers per commodity)
- the appropriate distribution for large portions (distribution based on kg/kg bw or kg/person)
- the appropriate expression of the large portion (as raw agricultural commodity, as raw edible portions or as processed product),
- the appropriate way to calculate, estimate or establish the cut-off point for the large portion from the distribution to get the desired level of protection or to protect the desired number of people (e.g. how to calculate a P97.5 for consumers only, what to do if the number of consumption values per commodity is too low)
- criteria for robustness of the large portion (minimum numbers of observations per country and per commodity)
- the appropriate procedure to follow if a large portion needs to be derived for a larger population than from which the food survey was derived (e.g. food survey from Netherlands for endive is used to predict consumption within EU and Codex or do we need a mixed database from several countries in the world?). One concern with using the highest LP size from across the world is that the quality of that data can vary across the world, especially if we are doing it country by country. The uncertainties around the 97.5th percentile consumption estimate – particularly for certain countries with less advanced dietary consumption capabilities -- might be very large. To the extent that a harmonized MRL is very dependent upon the estimate and that estimate "trumps" other estimates simply because it is the largest, this might prove problematic.

Further, a system, committee or working group is needed that sets out a call for data to update the large portions, evaluates the data submitted and organises a workshop to get agreement on the large portions. It is preferred to have a fixed large portion for a period of 10 years.

Appendix 5: Impact assessment for JMPR 2011 -2014 plant commodity MRLs, where the residue for dietary risk assessment is equal to the residue definition for enforcement and where the dietary exposure was > 20% ARfD

In 2015 RIVM performed a preliminary impact assessment on substances evaluated by the JMPR with the 2014 JMPR IESTI model for the current and option 1&2 and option 3 IESTI equations using the 2014 JMPR IESTI model.

JMPR; Year	Compound	Remark	Current HR/STMR v=1,3 U_e %ARfD	Option 1&2 MRL v=1,3 U_e %ARfD	Option 3 MRL v=1,3 no U_e %ARfD
2013	chlorpyrifos-methyl	wheat flour	80%	130%	130%
2013	chlorpyrifos-methyl	polished rice	120%	120%	120%
2012	dichlorvos	polished rice	130%	170%	170%
2012	dichlorvos	wheat flour	60%	180%	180%
2013	difenoconazole	grapes raw; grape juice	30%	70%	70%
2013	difenoconazole	potato total	30%	70%	80%
2014	Dimethomorph	head cabbage raw	40%	50%	50%
2014	Dimethomorph	lettuce leaf, total	110%	210%	240%
2014	Dimethomorph	spinach total	90%	220%	250%
2014	Dimethomorph	celery raw; celery juice	50%	80%	80%
2013	dithianon	grapes raw; grape juice	90%	340%	340%
2013	dithianon	apple, total; apple juice	40%	60%	120%
2013	dithianon	plums raw; dried plums	80%	110%	130%
2011; 2014	emamectin benzoate	lettuce, head	70%	110%	110%
2011; 2014	Emamectin benzoate	lettuce, leaf	100%	220%	250%
2011; 2014	Emamectin benzoate	Cos lettuce	40%	80%	80%
2014	Fenpropathrin	strawberry total	70%	120%	120%
2014	Fenpropathrin	apple, total; apple juice	390%	590%	1250%
2014	Fenpropathrin	raw cherries	140%	270%	270%
2014	Fenpropathrin	raw plums; dried	80%	110%	220%

JMPR; Year	Compound	Remark	Current HR/STMR v=1,3 U_e %ARfD	Option 1&2 MRL v=1,3 U_e %ARfD	Option 3 MRL v=1,3 no U_e %ARfD
		plums			
2014	Fenpropathrin	raw peach	190%	530%	590%
2014	Fenpropathrin	raw sweet peppers	70%	110%	110%
2014	Fenpropathrin	dried tomato	140%	210%	210%
2013	fenpyroximate	strawberry total, raw	50%	70%	70%
2013	fenpyroximate	raw plums; dried plums	80%	110%	130%
2013	fenpyroximate	raw cherries	50%	120%	120%
2013	fenpyroximate	raw cucumber	20%	60%	60%
2012; 2014	Fluopyram	raw head lettuce	40%	70%	70%
2012; 2014	Fluopyram	leaf lettuce, total	50%	190%	220%
2011	flutriafol	raw grapes; grape juice	80%	110%	110%
2012	imidacloprid	celery raw or celery juice	30%	50%	50%
2012	indoxacarb	lettuce leaf total	100%	190%	220%
2012	Phorate	potato total	290%	520%	630%
2014	Prothioconazole	cranberry total	3%	5%	5%
2014	Prothioconazole	currant juice	100%	190%	190%
2014	Prothioconazole	pumpkins raw or cooked	60%	80%	80%
2011; 2014	Pyraclostrobin	blueberry sauce	20%	50%	50%
2011; 2014	Pyraclostrobin	currant juice	30%	110%	110%
2011; 2014	Pyraclostrobin	strawberry total, raw	30%	50%	50%
2011; 2014	Pyraclostrobin	cherries raw	40%	70%	70%
2011; 2014	Pyraclostrobin	plums raw	30%	50%	110%
2011; 2014	Pyraclostrobin	artichoke total	50%	70%	70%
2011; 2013	sulfoxaflor	grapes raw, grape juice	40%	50%	50%
2011; 2013	sulfoxaflor	cabbage raw	3%	6%	6%

JMPR; Year	Compound	Remark	Current HR/STMR v=1,3 U_e %ARfD	Option 1&2 MRL v=1,3 U_e %ARfD	Option 3 MRL v=1,3 no U_e %ARfD
2011; 2013	sulfoxaflor	broccoli cooked	30%	50%	50%
2011; 2013	sulfoxaflor	leaf lettuce	60%	130%	140%
2011	tebuconazole	grapes raw; grape juice	100%	140%	140%
2013	tolfenpyrad	tea raw	80%	430%	430%
2013	triazophos	polished rice	1270%	17430%	17430%
2013	triflumizole	grapes raw	50%	90%	90%

Annex B – Stakeholder Meeting

Revisiting the International Estimate of Short -Term Intake (IESTI equations) used to estimate the acute exposure to pesticide residues via food (7 September 2015)

Summary

The stakeholder meeting started with a welcome address by Dr. Juliane Kleiner (EFSA, Head of REPRO Unit) followed by a welcome address by Dr.Angelika Tritscher (WHO, also on behalf of FAO). Subsequently, presentations[5] were given by

1. Angeliki Lysimachou, PAN Europe: 'Fundamental changes are needed in the calculations of dietary exposure to toxic pesticides to guarantee consumer's safety'
2. Monika Bross, BASF: 'Potential revision of the IESTI equation – an industry perspective[6]'
3. Volker Wachtler, European Commission, DG SANTÉ: 'Revisiting the International Estimate of Short-Term Intake (IESTI) : Considerations of the European Commission'
4. Panpilad Saikaew, National Bureau of Agricultural Commodity and Food Standards (Thailand): 'Thai experience on applying the acute risk assessment of pesticide residue'

In the afternoon, participants took part in a dialogue organized around seven round -tables. Each of the tables addressed a set of different question s, which was related to the questions in the Background document but was formulated at a more general level. In a second session, participants from one table reflected on the outcome of the first session from another table. The purpose of the round table sessions was to involve the participants in a so -called 'Socratic dialogue' where the purpose is not to convince but to question. It is not about right and wrong but about what is important, not about positions and arguments but about values and drivers. A Socratic dialogue does not drive towards a decision or uniform conclusion but towards mutual understanding. During the workshop on 8 and 9 September 2015 , it was checked whether the input from the Stakeholder Meeting round-table sessions was addressed in the discussions. Below, a summary is given of the outcome of the round -table sessions. Furthermore, it is indicated to which of the questions in the background document the input relates and therefore where it was used in the workshop discussions.

<u>Overall acceptance of the approach</u> (related to Chapter 3 in the Background document)

Question 1: The IESTI equations are used now for more than 15 years for performing acute dietary exposure assessments. Since their development some changes have been introduced (e.g. variability factors), but the basic concept is more or less unchanged. Taking into account the experience gained so far, do you think the IESTI equations are appropriate to ensure that consumers are not exposed to pesticide residue levels that would pose a health risk?

If you are of the opinion that the IESTI equations are not sufficiently fulfilling the purpose, what kind of modifications do you think would be appropriate?

What are the strengths/weaknesses of the IESTI equations?

Opinions of the participants of stakeholder meeting:

The actual equation works well, but at this stage needs to be revised for more transparency in term of risk communication.

A clear guidance and harmonized approach on how to derive some input parameters is needed. Examples: LP, consumption data quality (highly frequently consumed food items), how to deal with "low eaters" cases.

[5] The presentations are available on the EFSA website: http://www.efsa.europa.eu/en/events/event/150907

[6] Embedded in the presentation by Monika Bross, additional information was provided in the form of a document containing the responses from industry to the different questions in the Background document. Printed copies of this document were available during the Stakeholder Meeting. However, this document was not actively provided to the participants of the scientific workshop because it was considered to be inappropriate to give one stakeholder more impact than the other stakeholders. It is noted though that almost all participants to the workshop also attended the stakeholder meeting.

Use the MRL instead of HR because it is the legal value, it has to be safe. To conclude on a safe use you may be able to conclude on a safe MRL. Furthermore, HR is a single value it does not reflect a distribution as does the MRL.

Purpose and intended use of the MRL(related to Chapter 2 of the Background document)

Question 2A: (related to Chapter 2.1 in the Background document)

Food containing residues at the level of the adopted Codex MRL must be safe for the consumers. In other words, the acute exposure - MRL setting scenario should answer the question, whether the MRL allows for an appropriate level of protection for individuals eating a particular commodity with residues at the level of the MRL. Therefore: Do you think is it appropriate to use the MRL instead of the HR/STMR in the IESTI equation(s)? Can it be justified that the MRL is safe in the case the exposure at the level of the MRL exceeds the ARfD?

Opinions of the participants of stakeholder meeting:

Arguments against using the MRL:

- IESTI developed for use with HR and is already conservative, in other words, we should not use the MRL in the equations.

Arguments in favour of using the MRL:

- If residue levels present at the MRL need to be safe, then the MRL needs to be used because MRL is a more robust input parameter, better reflects the distribution of residue levels.
- Cannot be communicated nor justified to use the HR.

If change to MRL, modification of other parameters to be considered to maintain same level of conservatism.

Question 2B: (related to Chapter 2.2 to 2.4 in the Background document)

Although the IESTI equations are used by different national/international risk assessment bodies, the input parameters used are not always the same (e.g. different variability factors, unit weights, large portions). Do you think it would be important to find agreement on using harmonized input parameters? Are some parameters more relevant for harmonization than others?

Opinions of the participants of stakeholder meeting:

Most critical parameters for harmonisation:

- MRL vs. HR;
- variability factor;
- residue definitions.

Difficult or even impossible (regional parameters):

- Unit weights;
- large portions;
- body weight.

Level of protection (related to Chapter 3 in the Background document)

Question 3A:

In the context of dietary risk assessment frequently the term 'level of protection' (LoP) is used. What is your perception of the meaning of level of protection?

Opinions of the participants of stakeholder meeting:

Stakeholders referred to two definitions:

- EFSA: Percentage of person days below the ARfD in normal life;
- ARfD should be the benchmark protecting every person. What is the chance that once in your life you will be exposed above the ARfD.

Major comments:

- With this definition the LoP differs from one pesticide commodity combination to the other.
- You cannot use it for preregistration, because no monitoring data are available.

Question 3B:

Do you think the level of protection that is achieved with the current IESTI equation is appropriate/too high/too low?

Opinions of the participants of stakeholder meeting:

In general the perception is that it is appropriate, but this is not based on facts.

Question 3C:

Do you think the estimation is overly conservative if we estimate all uncertainties at worst case level?

Opinions of the participants of stakeholder meeting:

General finding that the IESTI is conservative, but not overly conservative.

Using the MRL instead of the HR is not expected to make the system overly/far more conservative.

Question 3D:

Is the number of MRLs that would pass the dietary risk assessment in the new methodology (replacing the HR/STMR with the MRL) versus the old methodology providing some confidence that the LoP has not changed drastically, in other words is this number a reasonable measure for the change in LoP?

Opinions of the participants of stakeholder meeting:

Contradictory opinions were expressed:

- **No,** it is scientifically not just to link the LoP as defined by EFSA with the counting of MRLs lost and gained.
- **Yes,** the impact on the LoP is reflected by change in the number of pesticide commodity combinations failing to pass the IESTI equation.

<u>Unit weight</u>

Question 4A: (related to Chapter 2.5 in the Background document)

The unit weight refers to the weight of a single unit of a crop, e.g. the weight of one apple or one cauliflower. In the IESTI calculation, the unit weight value (U) affects the outcome in two ways. The U of the edible portion determines whether the Large Portion (LP; the portion that a high-end consumer will eat in a 24 h period) will be composed by more than one crop unit (Case 2a) or will be a portion of the unit (Case 2b) and subsequently determines which IESTI formula is applicable. Furthermore, the U of the raw agricultural commodity determines whether a variability factor is to be applied to the HR.

In practice, unit weight data are scarce, not comparable, and no clear guidance exists on how to derive them.

Is it reasonable to calculate the IESTI without applying the unit weight?

Opinions of the participants of stakeholder meeting:

- The unit weight is already not considered as necessary and used by certain countries.
- Removing the unit weight would imply that high consumers can consume all the commodities at a high residue level.
- It should be determined for which commodities the impact might be highest (e.g. figs).
- The use of unit weight implies large uncertainty.
- Modelling (simulation, DEEM versus MCRA) could be used to evaluate the impact of removing the unit weight from the IESTI equation.

Question 4B: (related to Chapter 2.5 in the Background document)

If you want to keep the unit weight, can you suggest how the required data can be obtained and harmonized?

Opinions of the participants of stakeholder meeting:

- A unique unit weight cannot be used at world level, a range should be used.
- Individual commodities may have a broad range of unit weights.
- It would be preferable that the specific unit weight is used for each country for which consumption data are available.
- It is possible that vulnerable population groups might consume different unit weights.

<u>Opinions for a new IESTI equation</u>

Question 5A: (related to Chapter 2.1 and 2.6 in the Background document)

In the background document, both HR and STMR are proposed to be replaced by the MRL. This has a particular impact on processed commodities, bulked or blended products (case 3) MRLs. The estimation will become more conservative and theoretical exposures at the level of the MRL will more often exceed the ARfD.

Do you think using the MRL in the IESTI equation case 3 would reflect a realistic scenario or should we correct for the bulking and blending?

Opinions of the participants of stakeholder meeting:

For bulked/blended commodities:

- for bulked commodities (e.g. cereal, pulses, oilseeds) use of STMR makes most sense;
- more confidence is needed on the level of bulking and blending;
- for any blended commodity there may be an issue when using STMR for RA that cannot be resolved with regard to MRL looked at by enforcement authorities;
- idea of changing MRL setting for bulked / blended commodities towards a level closer to STMR may be considered.

Question 5B: (related to Chapter 2.1, 2.6 and 2.8 in the Background document)

Do you perceive any specific concern using the proposed approach for case 3 other food products (e.g. animal products, processed products)?

Opinions of the participants of stakeholder meeting:

Processed commodities: diverging views

- No, every processed commodity should be assessed separately with the appropriate residue level (STMR-P and STMR).
- No, with case 3 commodities there is very often no risk to consumers and it seems not worth changing approach.
- MRL is set for raw commodities and is not appropriate for processed commodity assessment since it is perceived over-conservative.
- Yes, MRL is in general worst -case and should always be used as the best way to definitely protect consumers, processing factors to be applied to MRL where appropriate.

Milk is a blended commodity and STMR is currently used but monitoring is made on the bottle, i.e. milk MRL not STMR is looked at.

Impact assessment for an adjusted equation

Question 6: (related to Chapter 3.1 in the Background document)

How should a new methodology for estimating acute dietary exposure be implemented? Do you consider it necessary to assess the impact o f IESTI changes on all MRLs? Can a subset be sufficient? Are you confident that using the old and new equations in parallel may lead to careful impact assessment over time?

Opinions of the participants of stakeholder meeting:

- Time for implementation will be needed.
- The impact should be assessed on an small subset of substances , considering the following factors: most vulnerable age classes/groups, key food commodities, and substances closest to ARfD.
- It is not clear what will be measured in an impact asse ssment (overall level of protection, changes of MRLs, whether it is global/regional?).

In case of a pilot:

- When working in parallel, risk communication is an issue ; it can be difficult to work with two different estimates and then select which one should s elected for the risk characterization (comparison with ARfD).

Enforcement and monitoring

Question 7A: (related to Chapter 4 in the Background document)

The IESTI equations have been developed to be used in the framework of MRL setting. It turned out that there is also a need to perform exposure/risk assessments at enforcement level (food inspection services).

Do you think a revised IESTI equation would be suitable to cover both needs? Which modifications would be necessary to achieve this goal?

Opinions of the participants of stakeholder meeting:

General OK to use IESTI for enforcement (level playing field), provided that PFs and CFs are available.

Questions 7B:

Is the IESTI equation actually being applied in assessing enforcement and monitoring data in your country? If yes, do you encounter any problems? If not, what happens with produce containing residues above the MRL? Would you support the use of the IESTI in this context?

Opinions of the participants of stakeholder meeting:

In practice it is not always used for enforcement (esp. outside EU).

Over-all, the participants had the following expectations regarding the scientific

- Global harmonisation of the equations;
- Development of a roadmap describing the activities needed to reach that goal.